



Cost-effectiveness analysis of the YouScreen Trial: a modelling study

Report 15 August 2024

About this report

This report was prepared by a team of modellers and epidemiologists from the Daffodil Centre, the University of Sydney, a joint venture with Cancer Council NSW, in close collaboration with research scientists, health economists and public health experts from the King's College London.

The Daffodil Centre team was comprised of Xin An, Michaela Hall, Megan Smith, James Killen, Laura Sergeant and Karen Canfell.

The team from King's College London included Peter Sasieni, Mairéad Lyons, Anita Lim, Huajie (Lily) Jin and Kang Wang, Jo Gambell and Katie Deats.

Modelling in this report was undertaken by the Daffodil Centre team. The probabilistic sensitivity analysis on costs and utility weights was undertaken by Huajie (Lily) Jin and Kang Wang.

Contents

About this report	2
Contents	3
Summary	4
Tables	7
Figures.....	9
Background.....	11
Methods	12
Findings.....	31
Discussion	56
Additional tables	61
Appendix 1: Model calibration to England	90
Appendix 2: Additional exploratory scenarios	97
Appendix 3: Schematics of screening initiation under No YouScreen (status quo) and YouScreen scenarios	100
Appendix 4: Australian hysterectomy prevalence.....	102
Glossary	103
References	107

Summary

Background

In 2019, England transitioned their national cervical screening programme from primary cytology to primary HPV testing. Primary HPV testing opens the possibility of using a self-collected vaginal sample for screening (self-sampling) which has been shown to increase screening participation amongst cervical screening non-attenders (never-and under-screened women). YouScreen is the largest self-sampling trial conducted in the UK to date, and marked the first-time self-sampling was integrated into the NHS. The trial aimed to assess the potential to increase screening participation amongst non-attendee women in England through an offer of HPV self-sampling, via either direct mail-out of kits or opportunistic offering in GP primary care. Using YouScreen trial data in combination with simulation modelling to project longer-term outcomes, we evaluated the potential effectiveness and cost-effectiveness of offering self-sampling to all non-attenders in England.

Methods

Using a previously developed comprehensive model of HPV transmission, natural history, and cervical screening (*Policy1-Cervix*), we simulated cohorts of women in England of various ages, vaccination status, and screening history. The first stage of modelling estimated short-term outcomes (over 5 years) of an intervention offered in 2021 (based on the YouScreen protocol), to compare with the trial and project short-term cross-sectional results from the five London boroughs where YouScreen was conducted. The second stage of modelling evaluated cost-effectiveness by estimating lifetime outcomes in various single birth cohorts under five sets of assumptions: (1) a counterfactual scenario without any cervical screening (to characterise the burden of disease without any intervention), (2) a scenario with no self-sampling offered (current practice in England); and three models of offering self-sampling to non-attenders, as per the YouScreen trial protocol: (3) via direct mail-out, (4) via an opportunistic offer to those attending GP primary care, and (5) via a combination of these two models (as occurred in YouScreen). Cost-effectiveness was assessed considering an indicative willingness to pay threshold (WTP) of £20,000-£30,000 per additional QALY gained, per UK National Institute of Clinical Excellence (NICE) guidelines for value-for-money. These scenarios and outcomes were simulated for a cohort of 100,000 unvaccinated women who turned 26 in 2021 (born in 1995). These women represent the youngest cohort of women who would have received the YouScreen self-sampling offer, and who would potentially benefit from YouScreen for the entire screening age range (25-64 years). Results were additionally scaled to the England female population in 2021, thereby allowing an estimate of outcomes that could have occurred in that year if the various scenarios had been operating in their steady state by then (i.e. for the lifetime duration of all females in the population). The impact of joint parameter uncertainty on both cost and quality of life (utility weights) data was simultaneously examined using a partial probabilistic sensitivity analysis (PSA).

Findings

Compared to the current practice scenario (i.e. no self-sampling), all three self-sampling models for under-screened women were predicted to reduce cancer cases and deaths. Over the lifetime (from age 9 to 84 years) of 100,000 women who turned 26 in 2021, and compared to current practice without self-sampling, the mail-out self-sampling model is predicted to prevent an additional 10 cervical cancer cases and 4 cervical cancer deaths (equating to relative reductions in cervical cancer cases and deaths 2.7% and 3.0% respectively); the GP opportunistic model is predicted to prevent 11 cervical cancer cases and 4 deaths (relative reductions of 2.9% and 3.4% respectively); and the combined model is predicted to prevent 17 cervical cancer cases and 4 cervical

cancer deaths (relative reductions 4.5% and 3.4% respectively). Had self-sampling for under-screened women been operating in England in 2021 (and reached steady state), compared with the current practice scenario without self-sampling, there would have been 2.1% fewer cervical cancer cases and 2.5% fewer cervical cancer deaths in the context of a mail-out offer only; 2.9% fewer cervical cancer cases and 2.6% fewer cervical cancer deaths in the context of a GP opportunistic model; and 5.1% fewer cervical cancer cases and 4.1% fewer cervical cancer deaths in the context of a combined mail-out and GP opportunistic model.

Assuming total HPV test delivery costs (including laboratory cost of £16.09 plus delivery costs) of £38.80, £25.51 and £19.65 for clinician-collected, direct mail-out, and YouScreen (GP opportunistic) HPV test costs respectively, we found that offering self-sampling to never- and under-screened women as per the YouScreen (GP opportunistic) pathway would be cost-effective for a cohort of unvaccinated women (ICER = £2,284 per additional QALY gained; range across uncertainty analyses: cost saving to £22,250 per additional QALY gained, encompassing the mean ICER estimate from the partial PSA on costs and utility weights only = £597). Self-sampling under the direct mail-out pathway was more effective than the status quo of screening without self-sampling; however, in both the main analysis and partial PSA across costs and QALY weights only, direct mail-out on its own was predicted to be both somewhat less effective and also more costly than the GP opportunistic model. A combined model of GP opportunistic and mail-out was also effective, and potentially cost-effective, compared to YouScreen (GP opportunistic) alone (ICER = £24,562 per additional QALY gained; range £12,169-£76,828, encompassing the mean ICER estimate from the partial PSA on costs and QALY weights = £19,580).

These findings were sensitive to some model input assumptions explored in sensitivity analysis, but in most cases, self-sampling scenarios became more favourable under the alternative assumptions compared to the baseline. Notably, compared to the baseline cost-effectiveness ratios for a cohort of unvaccinated women turning 26 in 2021, all self-sampling scenarios were comparatively more cost-effective for the two older cohorts (aged 41 or 56 in 2021). Additionally, we found the incremental cost-effectiveness ratios were more favourable when the lower bound cost for self-sampling is assumed, and even under several assumptions where the self-sampling scenarios were less effective than under the original assumptions (lower sensitivity of the HPV test on a self-collected sample; individuals using self-sampling continue to re-attend later rather than on time), because costs were also lower. The cost-effectiveness of the direct mail-out scenario was less favourable in the context of HPV vaccination (as in vaccinated cohorts overall costs are increasingly dominated by the cost of screening, which is relatively more expensive for direct mail-out due to wastage); however vaccination had relatively less effect on the cost effectiveness of the two strategies involving an opportunistic GP offer. Cost-effectiveness ratios were less favourable for the self-sampling scenarios when a substantially higher HPV test laboratory cost was assumed (£29, rather than £16.09). At this higher cost, the cost-effectiveness ratio (relative to the status quo without self-sampling) remained lower than £30,000 per additional QALY gained for the GP opportunistic model but exceeded £30,000 per additional QALY gained for the model which combined a GP opportunistic offer with direct mail-out. The incremental cost-effectiveness ratios were relatively stable when an alternative set of QALY weight assumptions was used (which assigned a disutility to negative screening test to reflect the experience of being screened, but with less disutility assigned to colposcopy referral and treatment for cervical precancer, compared to the baseline assumption) - because self-sampling induces more tests, and hence more negative tests, to occur compared to the status quo without self-sampling. The findings from the partial PSA on costs and QALY weights suggest there is a reasonably high certainty that a strategy involving an opportunistic GP offer would be cost-effective (80.2% probability at WTP £20,000 per QALY; 86.3% probability at WTP £30,000 per QALY), but less certainty regarding whether a GP opportunistic offer should be used on its own or in combination with direct mail-out. In the PSA on costs and

utility weights, the combined model had the highest Net Monetary Benefit (NMB), indicating it is expected to be the most cost-effective scenario at those WTP thresholds; however, results were uncertain, because the probability of the combined strategy being cost-effective at the £20,000 and £30,000 threshold was 0.421 and 0.474, respectively (compared to 0.381 and 0.389 for GP opportunistic alone). Additionally, the findings from the partial PSA were based on an HPV test laboratory cost that remained relatively close to the usual unit cost for clinician-collected samples (95% CI: £12.67 - £16.18), rather than the higher cost that occurred within the context of a trial (£29).

This evaluation of the effectiveness and cost-effectiveness of offering HPV self-sampling, either via direct mail-out, opportunistically through general practice, or both, found that all approaches were more effective than not offering self-sampling. Approaches involving an opportunistic offer via general practice, either alone or combined with direct mail-out, are likely to be cost-effective, but the cost-effectiveness of the combined model (and therefore whether it or an opportunistic offer through GPs alone is the preferred model) was sensitive to HPV test laboratory costs and the willingness to pay threshold. Provided HPV test laboratory costs are close to the usual unit cost for clinician-collected samples (£16.09), the combined model is potentially cost-effective but this becomes less likely if HPV test laboratory costs are very high (£29), demonstrating the importance of this cost.

A delivery model that relies exclusively on mail-out is unlikely to be cost-effective, as this model tended to be both more costly and less effective than offering self-sampling opportunistically through GPs. Our findings that introducing self-sampling for under-screened women at relatively older ages was even more cost-effective (or cost saving) than for those turning 26 underscores the importance of a rapid roll-out in the UK NHS Cervical Screening Programme to capture as many under-screened women as possible.

This evaluation, it is hoped, will enable informed evidence-based decision-making, and subsequent public communications, related to offering HPV self-sampling within England.

Tables

Table 1 Screening coverage assumptions (women aged 25-64 years) for scenarios modelled in Stage 1	14
Table 2 Modelled test characteristics for primary screening tests (for females aged 25 years and over)	19
Table 3 Itemised programme costs contributing to the calculation of an incremental cost-effectiveness ratio (ICER) for baseline scenario and scenarios considered in univariate uncertainty analysis.	22
Table 4 Utility weights contributing to the calculation of an incremental cost-effectiveness ratio (ICER).....	25
Table 5 Itemised programme costs contributing to the calculation of an incremental cost-effectiveness ratio (ICER) for baseline scenario and scenarios considered in probabilistic sensitivity analysis	27
Table 6 Description of uncertainty analysis.	29
Table 7 Summary of model findings (2021-2025) for status quo vs YouScreen five London boroughs included in the YouScreen trial (Barnet, Camden, Islington, Newham and Tower Hamlets).....	32
Table 8 Summary of the screening participation outputs.	35
Table 9 Summary of model findings for a cohort of 100,000 women aged 26 at entry (range includes total range generated by 1-way stochastic uncertainty analysis, excluding alternative cohorts)	37
Table 10 Summary of model findings – results scaled to England female population in 2021*	40
Table 11 PSA results: Mean total Costs, QALYs and ICER and associated 95% CI (per 100,000 women who entered screening when 25; offered YouScreen self-sampling from age 26).	52
Table 12 PSA results: cost-effectiveness and uncertainty.	54
Table 13 Summary of model findings for a cohort of 100,000 women turning 41 in 2021.	61
Table 14 Summary of model findings for a cohort of 100,000 women turning 56 in 2021.	63
Table 15 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 and who were offered HPV vaccination at age 12.....	65
Table 16 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when the lower bound of screening participation is assumed.....	67
Table 17 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when the costs and QALYs are undiscounted.	69
Table 18 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when the lower bound of test positivity matrix (TPM) is assumed.....	72
Table 19 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when no hysterectomy was ever performed.	74
Table 20 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when the YouScreen self-sampling kits are offered from one-year late.	76
Table 21 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when upper bound of HPV test costs are assumed.	78
Table 22 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when upper bound of all costs are assumed (see Table 3 for details).....	80
Table 23 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when lower bound of HPV and LBC tests costs are implemented.	82
Table 24 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when lower bound of all costs are implemented (see Table 3 for details).	84
Table 25 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when alternative disutility weights are implemented.	86
Table 26 Table of exploratory scenarios to demonstrate the impact of inputs on screening participation outputs.	97

Figures

Figure 1 Diagram of trial-based modelling of YouScreen trial as it occurred (GP opportunistic and direct mail-out combined)	15
Figure 2 Diagram of the Policy1-Cervix model platform ecosystem.....	18
Figure 3 Assumed HPV vaccination programme coverage in girls* (single-dose effective) for catch-up and mop-up (aged 14-19 years over 2008-2010) and routine cohorts and mop-up (routine in School Year 8, and mop-up in School Year 9 and 10).	21
Figure 4 Screening coverage comparison between the status quo scenario (based on five London boroughs' average screening coverage) and the screening coverage boosted by YouScreen trial, in year 2020 and 2021.	31
Figure 5 Policy1-Cervix modelled 3.5 and 5.5-yearly screening coverage versus observed data in 2022, by age of the cohort.	34
Figure 6 Costs versus quality-adjusted life years (both discounted at 3.5%) for four simulated scenarios over the lifetime of 100,000 women aged 26 at entry. Incremental cost-effectiveness ratios (ICERs) are calculated for scenarios falling along the efficiency frontier (thin line connecting scenarios)	36
Figure 7 Predicted age-specific (A) cervical cancer incidence and (B) cervical cancer mortality rates per 100,000 women.....	43
Figure 8 Predicted number of (A) HPV tests and (B) LBC tests by age, per 100,000 women.	44
Figure 9 Predicted number of (A) colposcopy evaluations, (B) biopsies, and (C) precancer treatments by age, per 100,000 women.....	45
Figure 10 Variation in cervical cancer (A) cases and (B) deaths prevented (compared to No YouScreen)† for three self-sampling scenarios, compared to cancer cases and deaths prevented in the baseline analysis, due to variation in a range of parameters*.....	46
Figure 11 Variation in additional total programme costs† associated with three self-sampling scenarios (compared to the No YouScreen scenario), due to variation in a range of parameters*.	48
Figure 12 Variation in the cost-effectiveness ratio for (A) Direct mail-out only, (B) YouScreen (GP opportunistic only), and (C) YouScreen (GP opportunistic and mail-out combined) scenarios relative to baseline scenario (No YouScreen), due to variation in a range of parameters.	50
Figure 13 Cost-effectiveness Plane: lifetime costs versus QALYs (discounted at 3.5% pa), over the lifetime of 100,000 women who entered screening when 25, and YouScreen self-sampling started being offered when they were aged 26.....	52
Figure 14 Cost-effectiveness Acceptability Curve (CEAC) and Cost-effectiveness Acceptability Frontier (CEAF).	55
Figure 15 Management of women at their primary HPV test (including follow-up in 12 months for hrHPV positive women with normal cytology).....	91
Figure 16 Management of women at colposcopy evaluation.	91
Figure 17 Management of women following colposcopy evaluation with abnormal findings.	92
Figure 18 <i>Policy1-Cervix</i> versus observed age-specific cervical cancer incidence (A) and mortality (B) rates per 100,000 women.....	93
Figure 19 <i>Policy1-Cervix</i> versus observed age-specific cervical cancer incidence rates at stages (A) FIGO IA/B (B) FIGO II/III and (C) FIGO IV, per 100,000 women.	94
Figure 20 <i>Policy1-Cervix</i> versus observed age-specific rates of (A) low-grade and (B) high-grade cytology per 1,000 women screened.	95
Figure 21 <i>Policy1-Cervix</i> versus observed age-specific HPV prevalence in England.....	96
Figure 22 Schematic of screening initiation under No YouScreen scenario.	100
Final Report August 2024 – CONFIDENTIAL RELEASE TO UKNSC	9

Figure 23 Schematic of screening initiation under YouScreen scenarios.	101
Figure 24 Australian hysterectomy prevalence. The age-specific probability of benign hysterectomy was derived from the 2001 and 2005 National Health Survey ^{41,42}	102

Background

Cervical cancer is the fourth most common cancer affecting women globally, with almost all (99%) cervical cancers being linked to human papillomavirus (HPV) infection. Vaccination against HPV is a highly safe and effective means of preventing HPV acquisition, and therefore cervical cancer. In addition, because a persistent HPV infection may progress slowly to cervical cancer through various precancer stages, cervical cancer is preventable through screening and precancer treatment. Cervical screening also enables early detection and treatment in women who have already developed a cervical cancer.

Due to the preventable (and treatable) nature of cervical cancer, in 2020 the WHO at the World Health Assembly adopted a global strategy to accelerate the elimination of cervical cancer. The strategy has three overarching pillars: (1) HPV vaccination for girls by age 15, (2) cervical screening (using HPV testing or a comparably accurate future test), and (3) treatment of identified disease (precancer and cancer). In many lower-middle income countries, these pillars of cervical cancer prevention will be implemented and scaled-up almost simultaneously. Within high-income countries however, vaccination, screening and treatment are often in place and the key activities are to scale up coverage to meet the targets, and to transition from cytology to HPV DNA testing, where this has not already occurred.

In England, cervical screening is available to women aged 25-64 years, at three-yearly intervals for women aged under 50 years and five-yearly screening for women aged 50 years and over. The national cervical screening programme in England has also recently completed a transition (in December 2019) from a primary cytology-based screening programme to HPV DNA testing. Cervical screening participation in England has been declining over the past 20 years, with recent (2022) coverage estimates 67.6% for women aged 25-49 having been screened in the last 3.5 years, and 74.6% for women aged 50-64 years having been screened in the last 5.5 years (NHS England Screening Quality Assurance Service 2023). In other settings, access to self-collected HPV testing where a female may collect a vaginal sample using a swab, has been shown to improve non-attendee participation in screening (Arbyn, Smith et al. 2018), and therefore a self-sampling pathway was integrated into the screening programme as part of an implementation feasibility trial (the YouScreen trial) ¹. Ultimately, the YouScreen trial offered kits to approximately 27,000 never screened and under-screened women. In YouScreen, self-sampling was offered to non-attenders (defined as never screened or at least 6 months overdue for cervical screening), systematically in a monthly mailout (for women unscreened at the 15-month anniversary of their last invitation) or opportunistically when they consulted a participating GP practice for any reason. Recruitment took place between 14th January 2021 and 30th November 2021, and returned self-samples were accepted for HPV testing until 31st January 2022. Notably, the YouScreen trial was conducted during, and therefore likely influenced by, the COVID-19 pandemic, as women may have been more reluctant than usual to attend for routine clinical services or had difficulty in accessing clinic appointments.

In the following analysis, we used data from the YouScreen trial provided by trial investigators and the *Policy1-Cervix* simulation model to conduct a modelled analysis to assess the effectiveness and cost-effectiveness of potential expansion of the YouScreen trial to never screened and under-screened women of the NHS cervical screening programme in England. Effectiveness and cost-effectiveness of offering self-collected HPV testing was assessed separately for mode of kit offer, i.e. direct mail-out or opportunistic offer in GP primary care.

Methods

Scenarios and outcomes measures

Using YouScreen trial data, we performed a cost-effectiveness analysis of a hypothetical expansion of YouScreen trial pathways (direct mail-out of self-sampling kits, opportunistic offering in GP primary care, and direct mail-out and GP opportunistic combined) to never screened and under-screened women of the NHS cervical screening programme in England.

We undertook the analysis in two stages. Firstly (Stage 1), a trial-based analysis which simulates multiple cohorts for a period of time and considers the entire age range that is affected by YouScreen trial. This approach incorporates all the age groups that are affected by the intervention, allows for validation against observed trial data and estimate the change in screening coverage at a population level during the time that the YouScreen trial was conducted. Secondly (Stage 2), a conventional approach to cost-effectiveness evaluation which simulates a single birth cohort and considers outcomes over a lifetime (but therefore requires additional assumptions about lifetime screening behaviour over multiple rounds, not obtainable from the trial). Additionally, we simulate a single cohort with a range of inputs to demonstrate the impact of these inputs on screening participation outputs and long-term outcomes.

Impact of YouScreen on screening participation

For all YouScreen scenarios, we assume an increase in both screening initiation (i.e., among women who were never-screened) and re-screening of late-screeners in response to the offer of self-sampling, which is relative to the background screening participation (see *Background screening participation*, page 20). YouScreen offers will be made over an entire screening interval (i.e., three consecutive years for women aged under 50, and, five consecutive years for women aged 50 years and over) to maximise the chances that women who become late during this period receive an offer.

We model a YouScreen sample return rate of 12.9% for women offered “direct mail-out”. We also model the proportion of women overdue screening who participate thanks to “YouScreen (GP opportunistic)” as 7.7%¹. Both rates are provided by YouScreen trial team for both the GP opportunistic and direct mail-out offer rates. The GP opportunistic offer considers the trial acceptance rate and the likelihood of women consulting GP primary care and being offered a self-sampling kit. To inform these assumed rates we utilised YouScreen trial data which are also provided by YouScreen trial team.

Part A: 5 London boroughs modelling, multi-cohort, giving extended time horizon trial outcomes

We simulated multiple cohorts (those aged 25-64 years at the start of the YouScreen trial in 2021) from 2020 to 2025 to capture the screening programme transitioning from cytology-based to an HPV based programme in 2020, the onset of the YouScreen trial in 2021, and the end of a five-yearly screening interval starting from 2021 (long enough to cover the screening interval for all women aged between 25 and 64). During the trial, YouScreen kits were offered either via direct mail-out or a GP opportunistic offer in five London boroughs (Barnet, Camden, Islington, Newham and Tower Hamlets.) To validate against trial data, we modelled four scenarios. All the scenarios assumed that in the absence of YouScreen, screening coverage was as observed in the five London boroughs (approximately 60% in 2018)². More specifically, the scenarios are:

¹ The 12.9% from “direct mail-out” is defined as a one-off acceptance rate, whereas 7.7% is an annual rate (among all those at least 6 months overdue screening).

1. Status quo - London boroughs: The status quo scenario assumes no self-sampling is offered to never- and late-screeners as well as the screening coverage of the five London boroughs. It was reported that the screening coverage in these areas (approximately 60%) is lower than the national average screening coverage in 2022 (69.6%); See Table 1 for modelling description in detail.
2. Mail-out only: assumes that self-sampling kits are only offered to non-attenders under the YouScreen trial protocol via the direct mail-out pathway.
3. YouScreen (Opportunistic only): assumes that self-sampling kits are only offered to non-attenders under the YouScreen trial protocol via the GP opportunistic pathway.
4. YouScreen (as it occurred): assumes that self-sampling kits are offered to non-attenders under the YouScreen trial protocol via both the GP opportunistic and direct mail-out pathways.

All the scenarios assumed the background screening coverage to be the average of screening coverage of the five London Boroughs; See Table 1 for modelling description in detail.

Table 1 Screening coverage assumptions (women aged 25-64 years) for scenarios modelled in Stage 1

Scenario	Sample type	2021	2022	2023	2024	2025
1. Status quo – 5 London boroughs	Clinician-collected sample coverage	Screening initiation and routine participation in the clinician collected CSP as observed in five London boroughs.				
	Self-sampling eligibility/uptake rate	None	None	None	None	None
2. Mail-out only – London Boroughs	Clinician collected sample coverage	Screening initiation and routine participation in the clinician collected CSP as observed in five London boroughs.				
	Self-sampling eligibility :					
	GP opportunistic:	None				
	Mail-out:	Women ≥12 months overdue for screening	Women who are newly 12 months overdue ²			
	Self-sampling uptake (among eligible) ^b	12.9%	0.5% ^c	0.5% ^c	0.5% ^{c,d}	0.5% ^{c,d}
3. YouScreen (Opportunistic only) – 5 London boroughs ^a	Clinician collected sample coverage	Screening initiation and routine participation in the clinician collected CSP as observed in five London boroughs.				
	Self-sampling eligibility :					
	GP opportunistic:	7.7%	7.7%	7.7%	7.7% ^d	7.7% ^d
	Mail-out:	None				
	Self-sampling uptake (among eligible) ^b	7.7%	7.7%	7.7%	7.7% ^d	7.7% ^d
4. YouScreen (Mail-out + GP opportunistic) boroughs ^a	Clinician-collected sample coverage	Screening uptake and routine participation in the clinician collected CSP as observed in five London boroughs.				
	Self-sampling eligibility :					
	GP opportunistic	Women ≥12 months overdue for screening				
	Mail-out	Women ≥12 months overdue for screening	Women who are newly 12 months overdue			
	Self-sampling uptake (among eligible) ^b	20.6% ^e	7.7% + 0.5% ^c = 8.2%	8.2%	8.2% ^d	8.2% ^d

a. As described in Figure 1.

b. Women who are eligible for self-sampling in this modelling are defined as women who are at least 12 months overdue as well as women who have never been screened (not initiated screening).

c. 0.5% is the percentage of women who are newly 12 months overdue and return a mail-out kit.

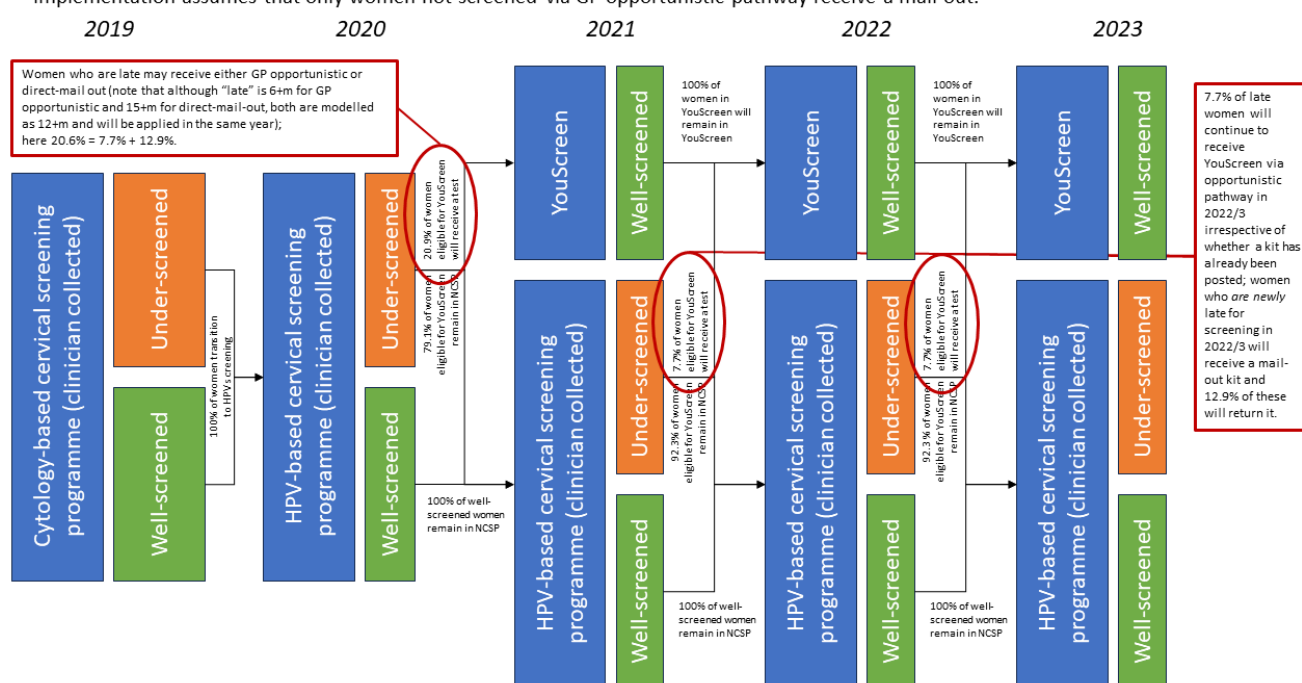
d. non-zero rates for women aged 50 and above, 0% for women aged between 25 and 49 years.

e. The self-sampling uptake rate 20.6% was calculated by adding annual rate of GP opportunistic offer 7.7% and acceptance rate of mail-out offer 12.9%.

We assume women who are non-attenders in 2021 may receive either GP opportunistic or direct mail-out (note that although in YouScreen being overdue for screening is being at least 6 months overdue for GP opportunistic and at least 15 months overdue for direct-mail-out, both are modelled as at least 12 months overdue and therefore will be applied in the same year). Combining the acceptance rate from direct Mail-out and the proportion of women overdue screening who participate thanks to the intervention (GP opportunistic only), we derive that there would be 20.6% of eligible women receiving self-sampling tests in 2021. In 2022 and 2023 (2024 and 2025 included if they are aged between 50 and 64), 7.7% of late women every year will continue receiving and returning the self-samples via GP opportunistic pathway regardless of whether a mail-out kit has already been posted. Additionally, women who are newly 12-month late during this time would be eligible to accept mail-out offer, and the rate of acceptance of the offer is still 12.9%.

Figure 1 Diagram of trial-based modelling of YouScreen trial as it occurred (GP opportunistic and direct mail-out combined)

Combined - NB “eligible” means late for screening by 6+ months (modelled as 12+ months). Note that the current implementation assumes that only women not screened via GP opportunistic pathway receive a mail-out.



Outcomes reported

The primary outcomes for the trial-based analysis at the multi-cohort/population level are:

- Additional women screened due to the YouScreen trial.
- Percent increase in screening participation (in 2021) due to the YouScreen trial.
- Additional CIN2+ detected during the YouScreen trial.
- Additional CIN3+ detected during the YouScreen trial.
- Additional costs due to the YouScreen trial.
- Incremental cost per extra woman screened, per CIN2+ detected and per CIN3+ detected.

² Note that although in YouScreen trial, being overdue for screening is being at least 6 months overdue for GP opportunistic and at least 15 months overdue for direct mail-out, the model (*Policy1-Cervix*) assumes the threshold of being overdue for both GP opportunistic and direct mail-out is at least 12 months.

To calculate absolute numbers, published estimates of the size of the female population were applied to age-specific rates of the relevant outcomes from the model. For the five London boroughs, the overall female population estimates for the boroughs were weighted according to the age distribution in England overall (as population estimates for the five boroughs were not available by both sex and 5-year age group). The total population of the boroughs are sourced from Greater London Authority ³, while the female population in the area is deduced using the national female-to-male ratio 51:49; See ⁴. The estimated number of women aged 25-64 years in 2021 was 393,673 for the five London boroughs.

Part B: exploratory modelling using a single cohort approach considering extension of the trial results to the whole population: lifetime cohort modelling

In the lifetime cohort modelling, for the 'No YouScreen' scenario, we assume that age-specific screening initiation and participation rates are aligned with the most recent (2022) reported data in England (see *Background screening participation*, page 20).⁵ For 'direct mail-out only', 'YouScreen (GP opportunistic)', and 'YouScreen (GP opportunistic and mail-out combined)', we assume an increase in both screening initiation (i.e., among women who were never-screened) and re-screening of late-screeners in response to the offer of self-sampling (see *Impact of YouScreen on screening participation*, page 12). YouScreen offers will be made over an entire screening interval (i.e., three consecutive years for women aged under 50, and, five consecutive years for women aged 50 years and over) to maximise the chances that women who may become late during this period receive an offer. We assume that women who are offered YouScreen mail-out kits and decline the offer will not receive any further YouScreen invitations and will continue to receive clinician-collected HPV tests if/when they would have otherwise received them. On the other hand, women who are offered YouScreen GP opportunistic offer and decline it, will be offered the GP opportunistic kits again 12 months later, and we assume the uptake rate for the self-sampling maintains.

Women who accept a YouScreen self-sampling offer are assumed to then be recruited into a "self-sampling" based programme for the rest of their screening lives, which runs alongside the usual clinician-collected screening programme with no overlap. Once recruited into this self-sampling programme, women are assumed to receive (and accept) offers for self-sampling each screening round. While in practice, these offers would be made when individuals become 6 or more months overdue for screening, the model operates on an annual timestep and therefore these women are assumed to receive the offer when they are due. However, in uncertainty analysis we consider an alternative assumption where the self-sampling offer is made (and accepted) when women become one-year overdue for their next routine screening test. Additionally, it is important to note that self-collected HPV tests under the YouScreen screening pathways are not available to women beyond the screen end age of 64 years, while women under clinician-collection pathway are still receiving regular tests when they are aged above 64 (shown in the national screening coverage in National Health Service England 2022). Therefore, it is possible that women in the No YouScreen pathway will receive additional screening tests not offered to YouScreen women.

In the exploratory scenarios, we provide a single-cohort analysis of long-term outcome. The cohort we simulate for this analysis is those aged 26 in 2021, and therefore women in this cohort can only be late for screening in 2021-2023 if they have failed to initiate screening; we therefore model a YouScreen acceptance rate of 12.9% for women offered "YouScreen (direct mail-out)" and 7.7% for women offered "YouScreen (GP opportunistic)". To achieve the single-cohort analysis, we performed a cost-effectiveness analysis of a hypothetical expansion of YouScreen trial pathways (direct mail-out of self-sampling kits, GP Practice-facilitated opportunistic offering,

and a combined approach) to never screened and under-screened women of the NHS cervical screening programme in England.

Scenarios

We simulated five screening scenarios for a cohort of unvaccinated women aged 26 in 2021 in England, including (1) A counterfactual “no screening” scenario which assumes that no cervical screening is offered, (2) “No YouScreen” i.e. self-sampling is not offered to never- and late-screener, (3) “Direct mail-out only” i.e. never- and late-screener are offered self-sampling under the YouScreen trial protocol via the mail-out pathway, (4) “YouScreen (GP opportunistic)” i.e. never- and late-screener are offered self-sampling under the YouScreen trial protocol via the opportunistic pathway, and (5) A scenario where both GP opportunistic and direct mail-out are offered, consistent with YouScreen as it occurred.

Outcomes reported

The primary outcomes for the cost-effectiveness analysis (CEA), over the lifetime of a cohort of 100,000 women aged 25, up to when they are aged 84 years, are:

- Incremental cost-effectiveness ratio (ICER) (i.e. incremental cost per quality-adjusted life-year [QALY] gained).
- Screening programme costs (from the perspective of the NHS and personal social services) per woman screened and per CIN2/3 detected.
- Additional women screened due to ongoing YouScreen.
- Additional CIN2+ detected due to ongoing YouScreen.
- Additional CIN3+ detected due to ongoing YouScreen.
- Number of cervical cancer cases and deaths, by age, accrued per 100,000 women.
- Resource utilisation volumes, per 100,000 women, including the number of HPV tests, cytology tests, colposcopy evaluations, biopsies, and pre-cancer treatments.

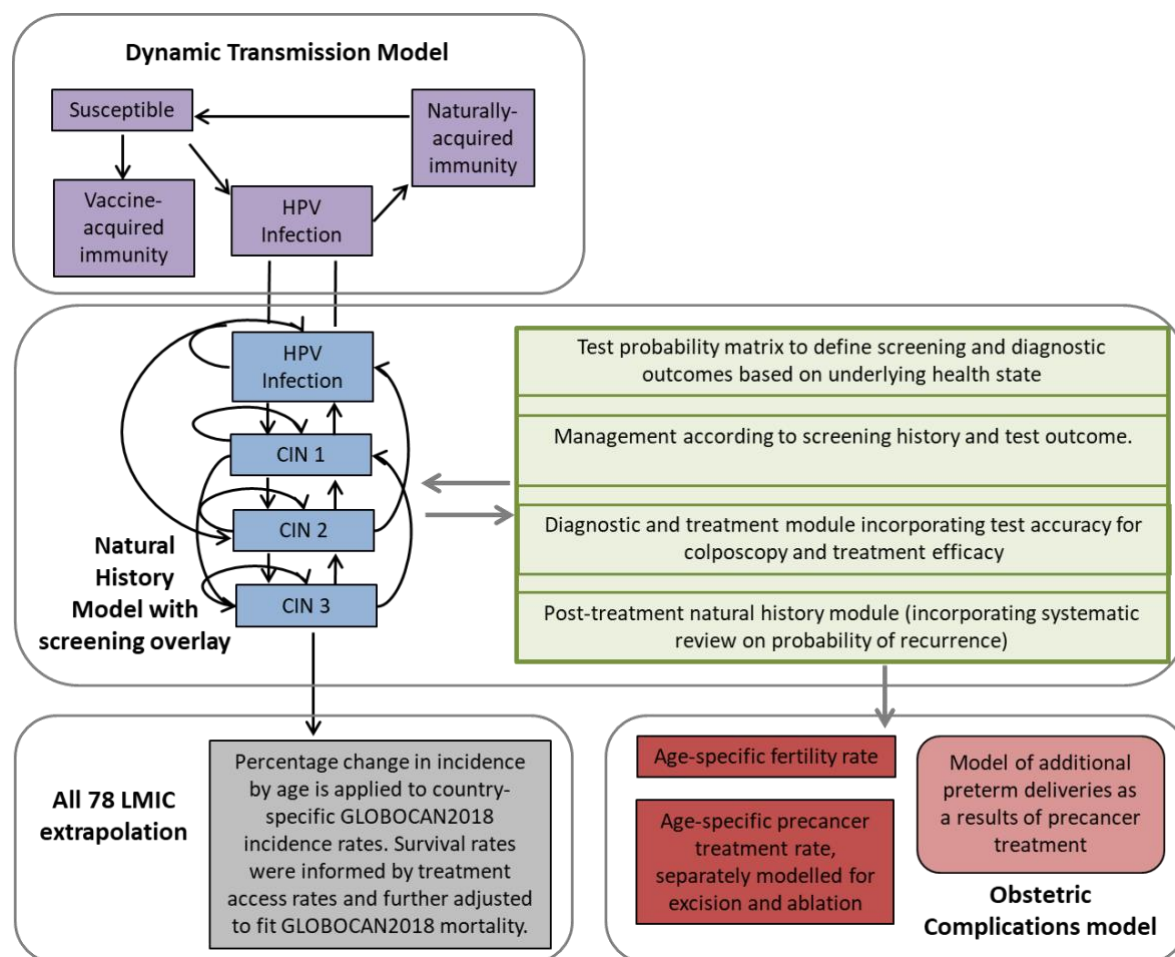
For selected parameters, one-way and probabilistic uncertainty analysis have been performed, with details provided below in the subsection titled *Uncertainty analysis (parameters and alternative scenarios)*.

Model structure and assumptions

Model description

We use the *Policy1-Cervix* platform, an extensively validated dynamic model of HPV transmission, vaccination, type-specific natural history, cancer survival, screening, diagnosis and treatment, to simulate the life-time costs and health outcomes following each of the screening strategies (Figure 2). The *Policy1-Cervix* platform has been used to evaluate the impact of elimination targets on cervical cancer incidence and mortality for all 78 LMIC in the Cervical Cancer Elimination Modelling Consortium (CCEMC) ^{6,7}, predicting the timeline to elimination of cervical cancer for 181 countries ⁸, and for countries such as the USA ⁹ and New Zealand ¹⁰. Recently, this model component has been used to evaluate the impact of the transitioning from cytology-based to an HPV-based screening program on cervical cancer elimination ¹⁰, resource utilisation volumes ¹¹, and health outcomes in Australia ¹².

Figure 2 Diagram of the Policy1-Cervix model platform ecosystem



The *Policy1-Cervix* platform has been adapted and parametrised to simulate the current estimated burden of HPV cervical disease in England. Specifically, we have updated the model for cervical screening (including assumed management according to screening history and test outcomes, and test positivity matrices), with the new assumed structure of screening management outlined in the section titled “Cervical screening programme management”, and, project-specific HPV test positivity is outlined in Table 2. England-specific age- and type-specific HPV incidence has been calibrated to match observed HPV prevalence, precancer and cancer outcomes in England. The process of model calibration and validation involves comparison of model predictions to observed data, including HPV prevalence, screening outcomes (including LSIL and HSIL cytology), cervical cancer incidence, and cervical cancer mortality. Calibration outcomes are reported in Appendix 1: *Calibration to England*.

Test-positivity assumptions

Assumed HPV and cytology test characteristics have been developed and validated against a range of data sources.¹³ For each underlying health state (that is, a woman’s true health state which is not observable – among well/no HPV, HPV infection, CIN1, CIN2, CIN3 and cervical cancer) a different probability of test positivity is assumed; therefore, simulated sensitivity and specificity result from a combination of the assumed

test positivity rates and the underlying health state distribution of a population, which varies with both time and female age. The assumed test characteristics, in addition to underlying test positivity rates, are described in Table 2.

Table 2 Modelled test characteristics for primary screening tests (for females aged 25 years and over)

Test type	Sensitivity/specificity	Test positivity (by underlying unobserved health state)
Primary HPV (clinician collected) ^a	Sensitivity (CIN2+): 96-98% Specificity (CIN2+): 78-98%	Well: 1.4% HPV: 44% CIN1: 84% CIN2: 93% CIN3+: 98%
Primary HPV (self-collected, baseline) ^b	Sensitivity (CIN2+): 95-97% Specificity (CIN2+): 78-98%	Well: 1.4% HPV: 44% CIN1: 83% CIN2: 92% CIN3+: 97%
Primary HPV (self-collected, worst-case uncertainty analysis) ^b	Sensitivity (CIN2+): 77-79% Specificity (CIN2+): 82-98%	Well: 1.4% HPV: 35% CIN1: 67% CIN2: 74% CIN3+: 79%
Primary cytology (pLSIL or worse)	Sensitivity (CIN2+): 75-89% Specificity (CIN2+): 89-96%	Well: 3.3% HPV: 7.8% CIN1: 39% CIN2: 65% CIN3: 84% Cancer: 100%

^a Test positivity assumptions for HPV DNA testing (clinician collected) are based on extensive model calibration of underlying disease states to reported test characteristics. ^b Test positivity assumptions for the baseline self-collected HPV DNA test (and worst-case) assumptions are calculated assuming a 0.99 (and 0.8) relative positivity rate across all underlying health states, relative to a test performed on a clinician-collected sample.

Population assumptions

For the trial-based analysis, we simulated the population of the 5 London boroughs that entered the trial scheme, the model uses the total female population from these boroughs. The population of the London boroughs are sourced from ³. Due to the lack of age-specific population structure, we are applying the age structure of England female population to the population of boroughs of interest.

For the exploratory/lifetime analysis, we simulated a population of 10,000,000 unvaccinated females who turned 26 in 2021 (born in 1995); this cohort was chosen as it is the youngest cohort of women who would have received the YouScreen self-sampling offer, and who would potentially benefit from YouScreen throughout their lifetime. In uncertainty analysis, we consider alternative cohorts which would not experience YouScreen until later-on in their lifetime, and who are likely to have a screening history of cytology, including those aged 41 and 56 in 2021 (born in 1980 and 1965). As part of this uncertainty analysis, we additionally considered the impact of England's national HPV immunisation programme roll-out on these cohorts. Results are presented per 100,000 women.

Model parameterisation

The model platform contains direct data-informed input parameters specific to England, these estimates for all-cause mortality, screening participation, and HPV vaccine uptake. For parameters such as hysterectomy rates, where data from England were not available in the timeframe for this analysis, we used Australian hysterectomy data (see Figure 24, page 102), due to both Australia and England are high-income countries and have similar population structure and public health system. A sensitivity analysis was carried out to ascertain if hysterectomy assumptions affected model conclusions.

All-cause mortality

Age- and year-specific all-cause female mortality rates, spanning from 1950 to 2070 were sourced from the United Nations 2019 World Population Prospects Abridged Life Table, where predictions for mortality from 2020 onwards are based on the medium fertility variant ¹⁴.

Hysterectomy rates

Age-specific hysterectomy rates for England were not available in the timeframe for this analysis, and so the model assumed underlying age-specific hysterectomy rates consistent with data from Australia (see Figure 24). To assess the impact of hysterectomy assumptions, in the uncertainty analysis we considered a counterfactual “no hysterectomy” scenario.

Background screening participation

England’s national cervical screening programme transitioned from primary cytology with HPV triage (3-yearly for women aged 25-49 and 5-yearly for women aged 50-64) to primary HPV DNA testing with LBC triage (also 3-yearly for women aged 25-49 and 5-yearly for women aged 50-64). *Policy1-Cervix* platform modelled the screening programme transitioned from primary cytology to primary HPV DNA test in 2020.

Screening in the model is simulated accounting for an age-specific proportion of women who will initiate screening each year, in combination with the proportion who re-attend for their routine screening test, which is based on their age, the number of years since their last test and the recommendation given at this test. In the single cohort modelling, age-specific rates of women attending for their first ever screening test are based on 2022 published age-specific rates screening uptake in England; re-attendance behaviour is calibrated to National Health Service estimates of three-yearly and five-yearly participation in cervical screening by age-group.⁵ In the trial-based analysis where the background screening coverage is assumed to align with the 5 London boroughs, the model is calibrated to fit the average screening coverage of the area in 2018 (provided by YouScreen Protocol). Since the age-specific attendance rate of these boroughs is lacking, the calibrated screening coverage also manages to maintain age-specific pattern of the national screening coverage in 2022.

Women who test positive for HPV at their primary screening test, with negative or low-grade cytology, are assumed to return in 12-months for subsequent follow-up, with a re-attendance rate of 86.1% ¹⁵.

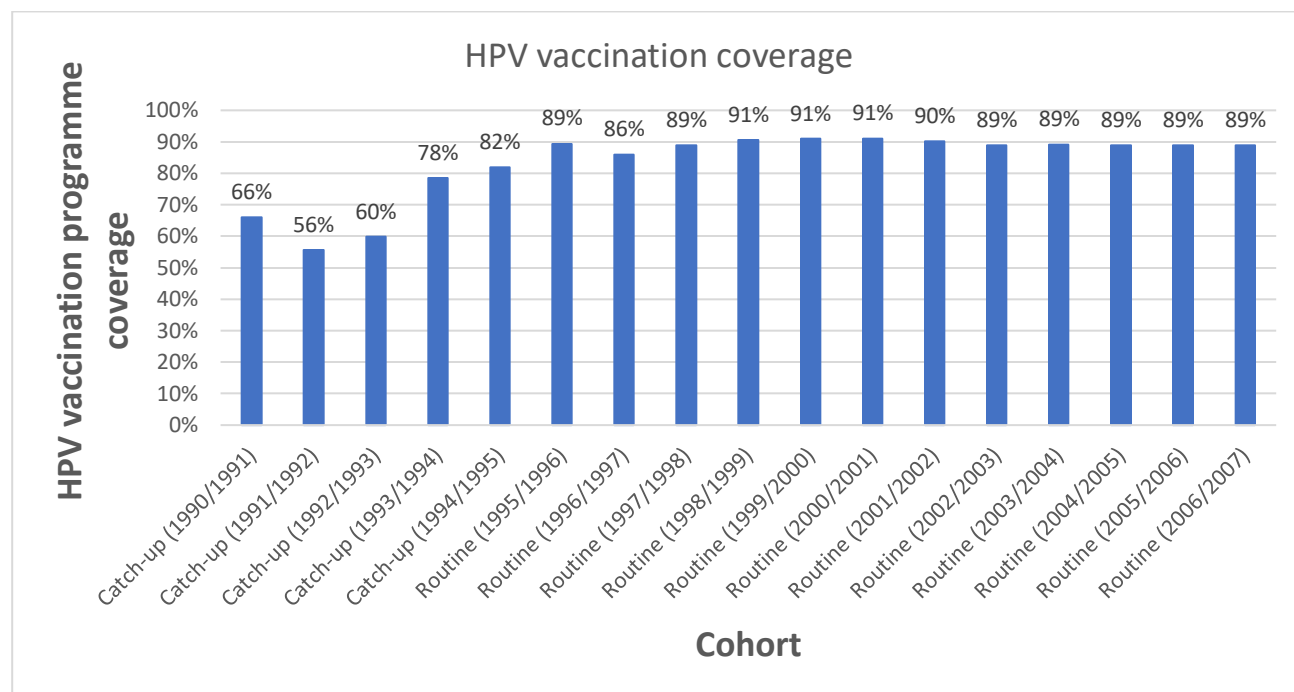
HPV immunisation programme features and coverage

It is important to note that for baseline scenarios, the modelling assumes that simulated cohorts are unvaccinated. However, in order to calibrate the model and ensure that we are effectively representing HPV and cervical precancer prevalence and detection as it currently is in England, it was necessary to incorporate the HPV vaccination programme characteristics. Scenarios which do consider the impact of the YouScreen trial in HPV vaccinated cohorts are considered in uncertainty analysis.

Human papillomavirus (HPV) immunisation with a bivalent vaccine (HPV 16/18) was introduced in England on 1st Sept 2008, with routine vaccination offered to girls aged 12 – 13 and catch-up programme for females aged up to 18 years over 2008-2010¹⁶. In 2012 the bivalent HPV vaccine was replaced with a quadrivalent HPV vaccine (HPV 6/11/16/18), and in September 2019 males were added to the HPV vaccination programme¹⁷.

For validation scenarios, and vaccination scenarios considered in uncertainty analysis, we simulated the direct and herd-effects due to HPV vaccination in England. Due to the annualization of the model, the commencement of HPV vaccination with a vaccine protecting against HPV types 16 and 18 (no cross protection of non-vaccine included types) is modelled from 2009 onwards, with the adoption of the quadrivalent HPV vaccine from 2012. The addition of males to the national HPV vaccination programme from September 2019 was not modelled in this analysis, given that this is not expected to influence cervical cancer risk in any of the simulated cohorts, with the youngest cohort turning 26 in 2021. We assume 100% lifelong protection against infection against vaccine-included HPV types in vaccinated individuals.

Figure 3 Assumed HPV vaccination programme coverage in girls* (single-dose effective) for catch-up and mop-up (aged 14-19 years over 2008-2010) and routine cohorts and mop-up (routine in School Year 8, and mop-up in School Year 9 and 10).



*Coverage data for years 2008/09-2013/14 was obtained from a 2015 coverage report¹⁶, and data for years 2014/15-2020/21 was obtained from the online database published by UK Health Security Agency (2022).

Calculating costs, quality-adjusted life-years and cost-effectiveness

We calculated incremental cost-effectiveness ratios (ICER) per quality-adjusted life-year saved, in addition to incremental programme costs per women screened and per CIN2/3 detected. Costs are from NHS and personal social services, with costs and QALYs discounted at 3.5% from the time of intervention. Exact values for itemised programme costs, and disutility associated with screening, precancer detection, cancer detection and cancer treatment are described in Table 3 and Table 4 respectively; all costs have been inflated to 2022.

Unpublished costs data in Table 3

In order to assess cost effectiveness with a reasonable assumption of cost and without knowing or
Final Report August 2024 – CONFIDENTIAL RELEASE TO UKNSC

compromising the commercial sensitivity of laboratory costs, a modelling exercise was carried out based on the public tender documentation for the commissioning of laboratory cervical screening services in England. Using the publication of contract award cost information and with an activity modelling template provided by the NHS Cervical Screening Programme, the YouScreen team calculated an upper and lower bound of costs for HPV tests. An estimate and range for YouScreen HPV tests was provided. A reflex cytology cost was applied based on an average cost value for London in 2018 provided by NHS London. This approach provided the *Policy1-Cervix* model with values for the full stochastic modelling shown in Table 3 and was applied in the Probabilistic Sensitivity Analysis as shown in Table 5.

Table 3 Itemised programme costs contributing to the calculation of an incremental cost-effectiveness ratio (ICER) for baseline scenario and scenarios considered in univariate uncertainty analysis.

Parameter description	No YouScreen	YouScreen (direct mail-out)	YouScreen (GP opportunistic)
Primary HPV test (including consumables, personnel, overheads and postage costs where applicable) ^a	Baseline cost: £38.80 Includes: £16.09 laboratory cost (unpublished) + £22.71 sample collection cost (Irenjeet, Yoon Hong et al. 2019)	Baseline cost: £25.51 Includes: £16.09 laboratory cost + £2.38 notification letter and invitation + £3.56 test kit + £3.48 for tracked return to the laboratory (all unpublished).	Baseline cost: £19.65 Includes: £16.09 laboratory cost + £3.56 test kit (all unpublished)
	Upper bound cost assumption <i>(same as the baseline assumption):</i> £38.80 Includes: £16.09 laboratory cost (unpublished) and a £22.71 sample collection cost (Irenjeet, Yoon Hong et al. 2019)	Upper bound cost assumption: £38.42 <i>(assumes higher laboratory costs)</i> Includes: £29 laboratory cost. + £2.38 notification letter invitation. + £3.56 test kit. + £3.48 for tracked return to the laboratory from YouScreen trial (all unpublished)	Upper bound cost assumption: £32.56 <i>(assumes higher laboratory costs)</i> Includes: £29 laboratory cost + £3.56 test kit from YouScreen trial. (all unpublished)

Parameter description	No YouScreen	YouScreen (direct mail-out)	YouScreen (GP opportunistic)
	Lower bound cost assumption: lower laboratory cost £35.28 (£12.57 laboratory cost + £22.71 sample collection cost (Irenjeet, Yoon Hong et al. 2019)).	Lower bound cost assumption: £21.99 (<i>assumes lower laboratory costs</i>) Includes: £12.57 laboratory cost (Irenjeet, Yoon Hong et al. 2019) + £2.38 notification letter and invitation + £3.56 test kit + £3.48 for tracked return to the laboratory from YouScreen trial) (unpublished).	Lower bound cost assumption: £16.13 (<i>assumes lower laboratory costs</i>) Includes: £12.57 laboratory cost (Irenjeet, Yoon Hong et al. 2019) + £3.56 test kit from YouScreen trial. (unpublished)
LBC test cost associated with a positive primary HPV test (including consumables, personnel and overheads) ^b	Baseline cost: £25 (reflex LBC laboratory cost) (unpublished)	Baseline cost: £47.71 (£25 reflex LBC laboratory cost (unpublished) + £22.71 for sample collection at GP visit ¹⁸ .	Baseline cost: £47.71 (£25 reflex LBC laboratory cost (unpublished) with £22.71 for sample collection at the GP, ¹⁸ .
	Upper bound cost assumption is the same as the baseline assumption.	Upper bound cost assumption is the same as the baseline assumption.	Upper bound cost assumption is the same as the baseline assumption.
	Lower bound cost assumption: £21.91 ¹⁸	Lower bound cost assumption: lower lab cost £44.62 Includes: £21.91 reflex LBC laboratory cost + £22.71 for sample collection at GP visit ¹⁸ .	Lower bound cost assumption: lower lab cost £44.62 Includes: £21.91 reflex LBC laboratory cost + £22.71 for sample collection at GP visit ¹⁸ .
Colposcopy evaluation with biopsy	£216.50 (£176.00 - £257.00)	£216.50 (£176.00 - £257.00)	£216.50 (£176.00 - £257.00)
Precancer treatment (LEEP)	£205.00 (£205.00 - £309.00)	£205.00 (£205.00 - £309.00)	£205.00 (£205.00 - £309.00)
Precancer treatment (cone)	£162.00 (£162.00 - £249.00)	£162.00 (£162.00 - £249.00)	£162.00 (£162.00 - £249.00)

Parameter description	No YouScreen	YouScreen (direct mail-out)	YouScreen (GP opportunistic)
Cost of cervical cancer detection and treatment (localised) ^c	£4,346.32	£4,346.32	£4,346.32
Cost of cervical cancer detection and treatment (regional) ^c	£10,865.78	£10,865.78	£10,865.78
Cost of cervical cancer detection and treatment (distant) ^c	£19,939.99	£19,939.99	£19,939.99

- The total cost for kits sent but not returned in YouScreen (direct mail-out) scenario was calculated by multiplying the number of women who were eligible for self-samplings (Mail-out kits) and rejected the offer, with the item costs for notification letter invitation and test kit.*
- Under the current NHS tender for provision of cervical screening, the cost of a primary HPV test, without YouScreen, includes the cost of any subsequent reflex LBC. Under YouScreen women who are positive for a self-collected HPV test are assumed to attend a GP clinic for the collection of a triage LBC test which incurs additional cost (assumed equal to sample collection under the No YouScreen scenario).*
- Costs for the detection and treatment of cervical cancer are based on a previous analysis of the cost of cervical cancer treatment in England and are indexed to 2022.¹⁹*

In the scenarios involving direct mail-out, the cost of sending kits and invitations to women who did not return a sample for HPV testing (wastage) was taken into account in the full *Policy1-Cervix* model results as follows. First, in each year when self-sampling kits were mailed out, the number of women who were eligible for self-sampling but did not return a sample was calculated as: the number of women who were eligible for self-sampling minus the number of women who returned a self-sampling kit. This (number of women who did not return a sample) was then multiplied by the costs of notification letter/invitation and test kit, and the resulting amount, representing wastage costs, added to the overall costs for the year in which the kits were sent.

Women who were eligible for self-sampling consisted of women who were at least 12 months late for screening (including women who have never screened). In direct mail-out scenarios, it was assumed that those who returned the kit would thereafter always return a kit, and that no further kits would be mailed out to women who had previously been sent a kit and not returned it. As noted in the Table 1, self-sampling was offered over one round (three consecutive years for those aged 25-49 years; five consecutive years for those aged 50-64 years); in the first year kits are sent to those who are at least 12 months overdue for screening, and in subsequent years only to those who are newly 12 or more months overdue for screening. For those turning 26 in 2021 (the baseline cohort considered), self-sampling kits were only sent when they reached age 26, as everyone who was never-screened at 26 was eligible for self-sampling, and no additional women could newly become overdue in the following two years. In contrast, in the two older cohorts (aged 41 or 56 in 2021), additional women became 12 or more months overdue each year. Therefore, kits were sent out and there was an additional wastage amount applied in 2021 only for the cohort who turned 26 in 2021, over 2021-2023 for the cohort who turned 41 in 2021, and over 2021-2025 for the cohort who turned 56 in 2021.

Table 4 Utility weights contributing to the calculation of an incremental cost-effectiveness ratio (ICER)

Health state description	Duration (years) applied to the disutility	Baseline utility set		Utility set used for uncertainty analysis	
		Value	Data source	Value	Data source
Alive, with no screening event that current year	1	1	Assumed	1	Assumed
Negative screening test (reflects the experience of being screened)	1	1	Assumed	0.9998	²⁰
Abnormal test result and/or colposcopy procedure (no treatment for cervical pre-cancer)	1	0.994	²¹	0.9997	²⁰
Treatment for cervical pre-cancer	1	0.99	²¹	0.9996	²⁰
Cervical cancer detected at localised stage of disease	1	0.68	^{22,23}	0.76	^{24,25}
Cervical cancer detected at regional stage of disease	1	0.56	^{22,23}	0.67	^{24,25}
Cervical cancer detected at distant stage of disease	1	0.48	²²	0.48	²²
Cervical cancer survivor	1	1	Assumed	1	Assumed

Uncertainty analysis (parameters and alternative scenarios)

Results from the cost-effectiveness analysis were assessed for stability in a range of uncertainty analysis, including one-way and probabilistic uncertainty analyses. The parameters considered in one-way uncertainty analysis, their values, and the type of uncertainty analysis conducted are outlined in Table 6.

In addition to conducting one-way sensitivity analyses, parameter uncertainty around costs and utility weights specifically was explored using a partial probabilistic sensitivity analysis (PSA) approach. In PSA, uncertain parameters are characterised by probability distributions (as detailed in Table 5, based on parameter values and ranges shown in Tables 3 and 4). The process involves performing a Monte Carlo simulation, which includes the following steps:

- 1) Randomly sampling values from the assigned distributions for each parameter tested in PSA (in this partial PSA, these parameters were costs and utility weights).
- 2) Running the model with these sampled values to calculate the outcomes of interest (i.e., costs and QALYs for each strategy).
- 3) Repeating this process multiple times (3,000 iterations for this study) to generate a distribution of costs and QALYs for each strategy.

Following the guidance on uncertainty analysis provided by Briggs *et al.*²⁶, we used a Gamma distribution for cost and resource use data. Briggs *et al.* recommended using a Beta distribution for utility values as it is bound

to the 0-1 range. However, for this study, some disutility values retrieved from the published literature have small absolute values and narrow ranges. Therefore, other distributions, such as Gamma and uniform distributions, provide a better fit for these utility values and were used in the PSA. The sampled disutility values were checked for plausibility, ensuring they had a plausible mean, 95% confidence interval, and a range between 0-1, before being used in the PSA.

The key benefit of conducting a PSA is that it simultaneously accounts for uncertainty in multiple input values, providing a more comprehensive reflection of this uncertainty in the results. In non-linear decision models, where outputs are the result of multiplicative functions, PSA offers the best estimates of mean costs and outcomes. For this reason, the NICE methods guidelines recommend that, when possible, the preferred cost-effectiveness estimates should be those derived from PSA ²⁷.

In this analysis, overall costs for each of the 3,000 PSA runs were calculated by applying the sampled cost parameters for that run to the model predicted volume of items with costs associated (tests, cancer diagnoses) at each age, applying discounting, and then summing. Similarly, the overall QALYs for each of the 3,000 PSA runs were calculated by applying the sampled parameter values for utility weights to the model predictions volumes of events associated with a disutility (screening, colposcopy, precancer treatment, cancer diagnosis and related treatment) at each age, discounting, and summing.

Table 5 Itemised programme costs contributing to the calculation of an incremental cost-effectiveness ratio (ICER) for baseline scenario and scenarios considered in probabilistic sensitivity analysis

Parameter	Mean	SE	Distribution type	Generated lower 95% CI	Generated upper 95% CI
COST (£)					
Primary HPV test (including consumables, personnel, overheads, and postage costs where applicable)					
Laboratory cost	16.09	0.90	Gamma	12.67	16.18
Sample collection cost	22.71	0.23	Gamma	22.27	23.16
Notification letter and invitation, test kit, tracked return to the laboratory (direct mail-out)	9.42	0.09	Gamma	9.24	9.61
Test kit (GP opportunistic)	3.56	0.04	Gamma	3.49	3.63
LBC test cost associated with a positive primary HPV test					
Reflex LBC laboratory cost	25.00	0.79	Gamma	21.96	25.05
Colposcopy evaluation with biopsy	216.50	20.66	Gamma	177.90	258.83
Precancer treatment:					
LEEP	205.00	26.53	Gamma	205.00	308.85
cone	162.00	22.19	Gamma	162.00	248.86
Cost of cervical cancer detection and treatment:					
localised stage	4,346.32	443.51	Gamma	3,520.69	5,257.61
regional stage	10,865.78	1,108.75	Gamma	8,801.72	13,143.99
distant stage	19,939.99	2,034.69	Gamma	16,152.21	24,120.78
DISUTILITY					
Negative screening test	0.000	0.0001	Uniform	0.0000	0.0002
Abnormal test result and/or colposcopy procedure	0.006	0.0015	Gamma	0.0010	0.0067
Treatment for cervical pre-cancer	0.010	0.0024	Gamma	0.0016	0.0111
Cervical cancer detected at:					
localised stage	0.320	0.0204	Gamma	0.2425	0.3225
regional stage	0.440	0.0281	Gamma	0.3334	0.4434
distant stage	0.520	NA	Fixed	NA	NA

Abbreviation: SE, standard error. Note: Utility values usually fit into the beta distribution, but because of the small absolute values of disutilities and their narrow ranges, Gamma distribution provides better fitness.

Based on the 3,000 PSA runs, we calculated 95% confidence intervals (CI) for costs, QALYs, and ICERs, for each strategy to reflect the uncertainty around the mean values of each of these results. Although the 95% CI for the ICER can be calculated using the Jackknife approach^{28,29}, it can sometimes be nonsensical. For instance, interpreting a negative ICER is challenging without knowing which cost-effectiveness quadrant the values or estimates fall into (i.e. whether it is more effective with lower costs [strictly better] or less effective with higher costs [strictly worse] than the relevant comparator). Even with a positive ICER, it is essential to know which intervention has the higher cost and QALY to correctly understand the cost-effectiveness, as the comparator could be either intervention. Therefore, additional methods were employed to visualise findings i.e., the cost-effectiveness plane (CEP, as also used in the main analysis), cost-effectiveness acceptability curves (CEACs), and

the cost-effectiveness acceptability frontier (CEAF) based on the net monetary benefit (NMB) approach ³⁰, defined as follows.

The CEP scatter plots display the calculated (expected) cost and QALY pairs for all simulations. If there are only two strategies, the ICER can be easily illustrated on the CEP with the cost difference on the vertical axis and the QALY difference on the horizontal axis. However, when comparing more than two strategies, as in the YouScreen study, the axes represent the absolute values of cost and QALY rather than the differences between strategies. This is because it is impractical to show the differences for all combinations of strategies, making direct comparisons difficult. Additionally, there is a risk that overlapping dots on the plot may occur due to minor differences between strategies, which can make interpretation challenging.

For multiple strategies, CEACs are useful for plotting each strategy's Bayesian probability of being cost-effective at various cost-effectiveness thresholds ³¹. The probability was calculated as follows: in each of the 3,000 simulations, the total cost (C) and total QALYs (Q) were estimated for each strategy. For a specific cost-effectiveness threshold (λ), the net monetary benefit (NMB) was calculated as $NMB = \lambda * Q - C$. The strategy with the highest NMB in each simulation was identified, and the probability of each strategy being cost-effective was the proportion of simulations in which that strategy had the highest NMB. CEACs were then created by plotting these proportions (y-axis) against different λ values (x-axis). The probability of each scenario being cost-effective and their NMBs will be highlighted at the threshold of £20,000 and £30,000, which are the willingness-to-pay thresholds suggested by NICE ³².

When interpreting the results of a PSA, it is important to note that the aim is to quantify the overall impact of joint parameter uncertainty. To achieve this, we assigned distributions to each parameter with a reasonably wide standard error. This approach tests the robustness of the results under all possible scenarios, including extreme cases, by considering all potential combinations of different values for each parameter. Consequently, based on the PSA results, it is not unusual to observe that even some interventions that are dominated in deterministic analysis could still have a small but non-zero probability of being cost-effective. In addition, Claxton et al. ³³ demonstrated that the strategy with the highest probability of being cost-effective (highest CEAC) at any given cost-effectiveness threshold may not necessarily be the most cost-effective choice. To maximise health gain, decisions should be based on the highest mean NMB, regardless of the associated probability. To address this limitation of CEACs, the CEAF can be plotted ³⁴.

Unlike CEACs, the CEAF focuses solely on the probability that the most cost-effective strategy is cost-effective across various thresholds. To achieve this, it is essential to identify the most cost-effective strategy at each threshold. This involves calculating the mean cost and mean QALY for each strategy over the 3,000 simulations and determining which strategy has the highest mean NMB at different WTP thresholds. This process helps identify the range of threshold values over which each strategy remains the most cost-effective, with WTP "switch points" indicating changes in which strategy is the most cost-effective and corresponding to the ICER between different strategies ³⁵. The lower end of this range marks the ICER for the specific strategy, while the upper end represents the ICER for the next more costly (and more effective) strategy.

Once the most cost-effective strategy for each threshold is determined, its probability of being cost-effective can be plotted on the y-axis against different λ values on the x-axis. This probability, derived from the CEAC, indicates the likelihood of making a correct decision. The probability of making an incorrect decision (error probability) is calculated by one minus the CEAF probability at any given cost-effectiveness threshold ³⁶. It is important to note that since the CEAF only depicts the most cost-effective strategies, it may not always align with the strategy that has the highest probability of being cost-effective.

Table 6 Description of uncertainty analysis.

Area of uncertainty	Type	Baseline assumption	Alternative assumption or range considered in uncertainty analysis
Age and screening history of women prior to YouScreen offer	One-way stochastic	For all scenarios, we consider a baseline cohort which assumes that women are turning 26 in 2021; the first cohort of women eligible for YouScreen for the entirety of their cervical screening eligibility.	We consider two alternative birth cohorts of women (those turning 41 and those turning 56 in 2021). The self-sampling offer still occurs over 2021-2023/5, and these cohorts will experience a history of primary cytology testing.
HPV vaccination programme characteristics, including screening uptake by sex/cohort	One-way stochastic	No impact of HPV vaccination.	Assume direct and indirect effects of the current HPV vaccination programme in England (see HPV immunisation programme features and coverage).
Background screening behaviour, including initiation into cervical screening and routine attendance of women initiated in screening (in the absence of YouScreen)	One-way stochastic	Age-specific screening behaviour, including initiation of cervical screening and re-attendance following a negative routine screening test, has been calibrated in order to ensure that age-specific model estimates for the proportion of women screened at least once in the previous 3.5 and 5.5 years are aligned with the most recently published 2022 data, as described in Figure 3.	Lower background screening: Age-specific screening behaviour, including initiation to cervical screening and re-attendance following a negative routine screening test has been calibrated such that that age-specific model estimates for the proportion of women screened at least once in the previous 3.5 and 5.5 years are aligned with the most recently published 2022 data for the five boroughs in England with the lowest reported screening participation (average three- and five-yearly screening participation assumed to be 54% and 64% respectively).
Discounting assumptions for costs and quality-adjusted life-years.	One-way stochastic	Costs and QALYs are discounted at 3.5%.	Costs and QALYs are undiscounted.
Test sensitivity of the self-collected HPV test relative to HPV testing on a clinician-collected sample	One-way stochastic	Self-collected HPV test positivity rates (by health state) are 2% lower than HPV testing on clinician-collected samples (Table 2).	Self-collected HPV test positivity rates (by health state) are 20% lower than HPV testing on clinician-collected samples (Table 2).
Hysterectomy	One-way stochastic	Underlying age-specific hysterectomy rates are assumed to match Australian age-specific hysterectomy data.	Counterfactual “no hysterectomy” scenario to assess the impact of hysterectomy assumptions.

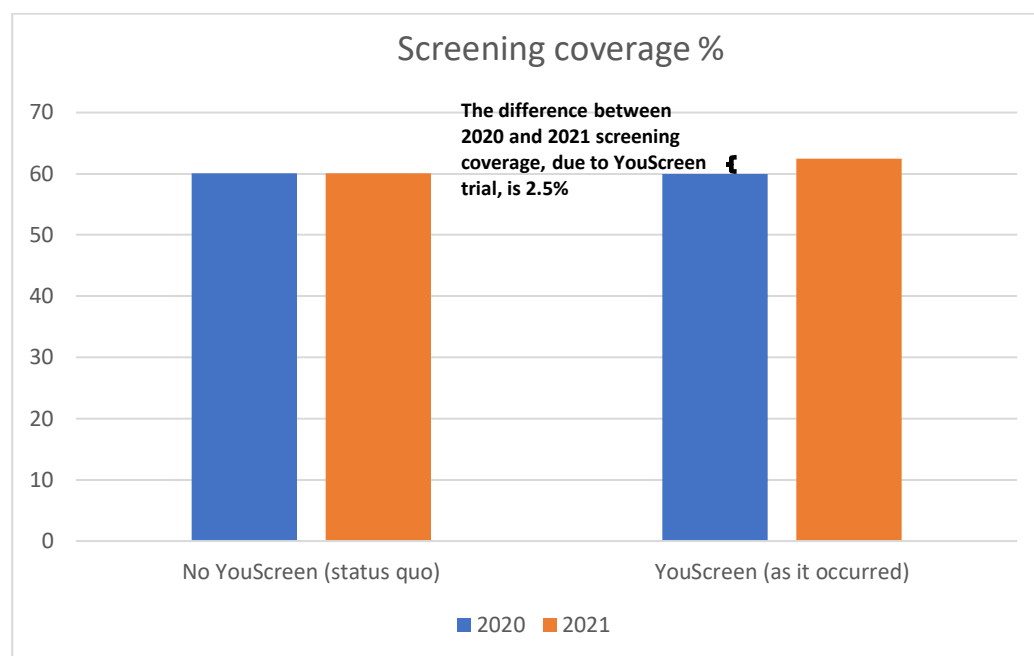
Area of uncertainty	Type	Baseline assumption	Alternative assumption or range considered in uncertainty analysis
Re-screening frequency of women who have accepted the YouScreen offer (applied to both YouScreen (direct mail-out) and YouScreen (GP opportunistic))	One-way stochastic	Women are assumed to have perfect on-time adherence to cervical screening (i.e., three-yearly when aged <50 and five-yearly when aged ≥50 years).	Women are assumed to always return 12 months late for cervical screening (i.e., four-yearly when aged <50 and six-yearly when aged ≥50 years).
Costs associated with cervical screening and follow-up	One-way stochastic & PSA (with QALY weights)	Refer to Table 3 for cost assumptions.	Refer to Table 3 for cost assumptions used in uncertainty analysis.
Disutility-weights associated with cervical screening, cervical precancer detection and treatment, and invasive cervical cancer and treatment.	One-way stochastic & PSA (with costs)	Refer to Table 4 for baseline disutility assumptions.	Refer to Table 4 for disutility assumptions used in uncertainty analysis.

Findings

Trial-based modelling results

The model predicted that, over a full 12-month period, YouScreen would have the effect of increasing screening participation by the end of 2021 by 2.5 percentage points, from 60.0% to 62.5% (Figure 4).

Figure 4 Screening coverage comparison between the status quo scenario (based on five London boroughs' average screening coverage) and the screening coverage boosted by YouScreen trial, in year 2020 and 2021.



Projected over a 5-year period, it was predicted that direct mail-out, YouScreen (GP opportunistic only), and YouScreen (direct mail-out and GP opportunistic combined)³ would increase the number of women screened at least once in that timeframe by 2.94%, 4.22%, and 6.81%, respectively. The 5-yearly screening coverage (for women aged between 25 and 64) by the end of 5-year period would be 63.00%, 64.50%, and 66.7% for the direct mail-out, YouScreen (GP opportunistic only), and YouScreen (as it occurred), respectively. It was also reported that direct mail-out, YouScreen (GP opportunistic only), and YouScreen (as it occurred) would increase CIN2+ (and CIN3+) detection by 8.51% (7.02%), 10.56% (9.65%), and 17.70% (15.40%), respectively (Table 7). The 5-year timeframe was too short to see a noticeable impact on cancer cases or deaths (apart from a small shift to earlier detection of some cancer cases).

Compared to No YouScreen (status quo), the total (discounted) costs over the 5-year period were predicted to be higher for all three scenarios: 4.05% higher for the direct mail-out only scenario, 4.66% higher for the GP opportunistic scenario, and 8.22% higher for the YouScreen (as it occurred) scenario. While total costs were lowest for the direct mail-out scenario, this scenario was associated with higher costs per additional CIN2+ detected than the other two scenarios (£3,568, compared to £3,312 for GP opportunistic and £3,478 for YouScreen (as it occurred)) and per additional CIN3+ detected (£6,163 for direct mail-out, compared to £5,164 for GP opportunistic and £5,710 for YouScreen (as it occurred)). Historically about a third of CIN3 progressed to

³ Scenario 4: YouScreen (as it occurred) is equivalent to YouScreen (direct mail-out and GP opportunistic combined).

invasive cancer over 15 years, so these results imply 40-100 additional cancer prevented over 15-20 years from implementing self-sampling for a single round of screening in the five boroughs ³⁷. Similar argument suggests approximately £1,800 per cancer prevented, if there was no early detection due to self-sampling being available (and a third of CIN3 were not treated and progressed to cervical cancer).

Table 7 Summary of model findings (2021-2025) for status quo vs YouScreen five London boroughs included in the YouScreen trial (Barnet, Camden, Islington, Newham and Tower Hamlets)

Outcome	Status quo – London boroughs (no YouScreen)	Mail-out only: London boroughs	YouScreen (GP opportunistic): London boroughs	YouScreen (as it occurred): London boroughs
Screening coverage (2021)	60.0%	61.0%	61.5%	62.5%
Disease detection:				
High-grade histology	2,373	2,591	2,643	2,829
CIN2+	2,572	2,791	2,844	3,028
<u>Additional CIN2+ detected due to YouScreen</u>	-	219	272	456
CIN3+	1,806	1,933	1,980	2,084
<u>Additional CIN3+ detected due to YouScreen⁴</u>	-	127	174	278
Cervical cancer cases	199	199	200	200
Cervical cancer cases prevented compared to “status quo”	-	0	-1	-1
Women screened*	275,180	283,260	286,781	293,918
Additional women screened due to YouScreen	-	8,080	11,602	18,738
HPV tests	327,271	342,782	346,874	360,867
Colposcopies	12,432	13,455	13,575	14,482
Biopsies	9,413	10,195	10,289	10,978
Precancer treatments	3,799	4,095	4,158	4,413
Total costs	£20,632,124	£21,464,761	£21,610,291	£22,355,997
Discounted measurements (3.5% discounting rate):				
Total costs	£19,291,617	£20,072,739	£20,191,341	£20,878,250
Additional costs due to YouScreen	-	£781,122	£899,724	£1,586,632

Outcome	Status quo – London boroughs (no YouScreen)	Mail-out only: London boroughs	YouScreen (GP opportunistic): London boroughs	YouScreen (as it occurred): London boroughs
Screening coverage (2021)	60.0%	61.0%	61.5%	62.5%
Disease detection:				
High-grade histology	2,373	2,591	2,643	2,829
CIN2+	2,572	2,791	2,844	3,028
<i>Incremental cost per additional women screened:</i>				
Total	-	£97	£78	£85
Primary screening costs†	-	£27	£24	£25
LBC test costs	-	£17	£13	£15
Colposcopy costs	-	£26	£20	£22
Biopsy costs	-	£20	£15	£17
Pre-cancer treatment costs	-	£7	£6	£6
<i>Cervical cancer treatment costs:</i>				
local stage	-	£0.25	£0.53	£0.47
regional stage	-	£0.02	-£0.11	-£0.50
distant stage	-	£0.38	-£0.50	-£0.31
<i>Incremental cost per additional case detected</i>				
CIN2+	-	£3,568	£3,312	£3,478
CIN3+	-	£6,163	£5,164	£5,710

Re-attendance rates after self-sampling tests are assumed to be perfect. The discounting rate is 3.5% per year.

* Women screened indicates the number of women screened at least once between year 2021 and 2025. † includes HPV test costs, and visit/ mailout costs

Lifetime cohort modelling results

Single-cohort screening participation by age

Age-specific 3.5- and 5.5-year screening participation rates, defined as the percentage of eligible women who were screened in the previous 3.5 and 5.5 years, are presented in Figure 5 for the No YouScreen, direct mail-out, YouScreen (GP opportunistic), and YouScreen (GP opportunistic and mail-out combined) scenarios, alongside the observed screening coverage in 2021 in England. The model-generated coverage for the YouScreen scenarios represents what would have been observed in 2021, had the YouScreen interventions been at steady-state (i.e. operating over the lifetime of all of those in the population aged 25-64 years. The screening participation among women aged 25-64 years in terms of those who are up to date with screening (screened in the last 3.5 years for ages 25-49; screened in the last 5.5 years for ages 50-64) is: 68.12% (66.6% 25-49 years; 70.8% 50-64 years) for no YouScreen; 72.76% (69.8% 25-49 years; 77.7% 50-64 years) for direct mail-out; 72.96% (70.0% 25-49 years; 77.9% 50-64 years) for YouScreen (GP opportunistic), and 74.35% (71.5% 25-49 years; 79.1% 50-64 years) for YouScreen (GP opportunistic and mail-out combined) (

Table 8).

Figure 5 Policy1-Cervix modelled 3.5 and 5.5-yearly screening coverage versus observed data in 2022, by age of the cohort.

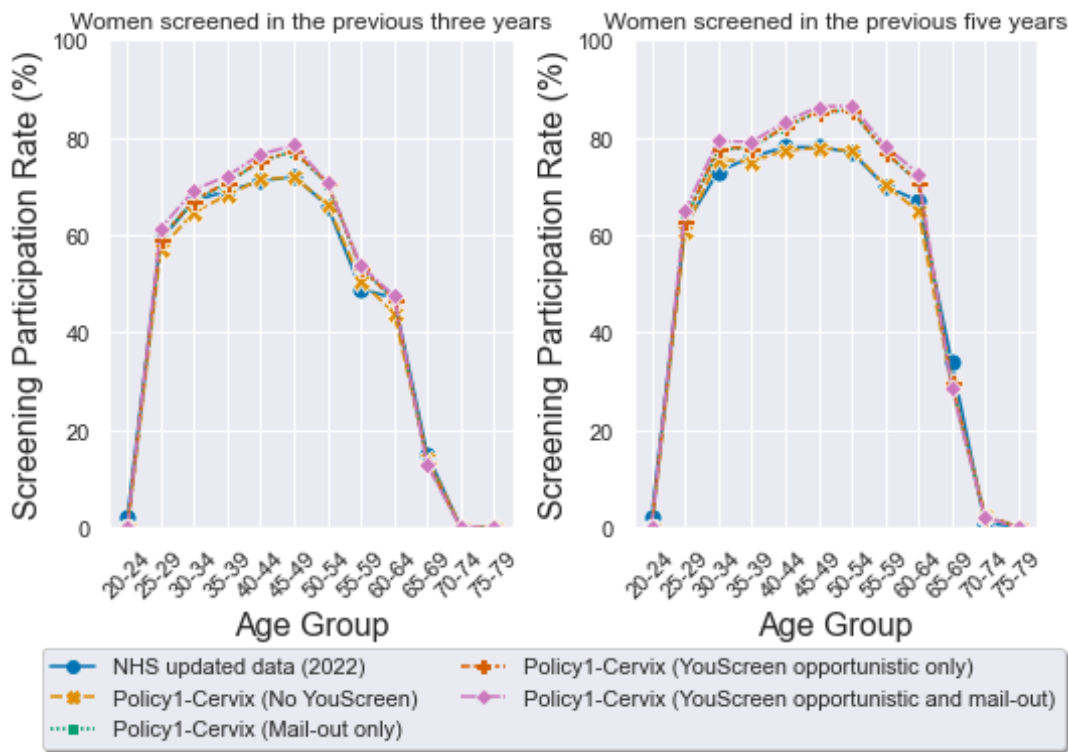


Table 8 Summary of the screening participation outputs.

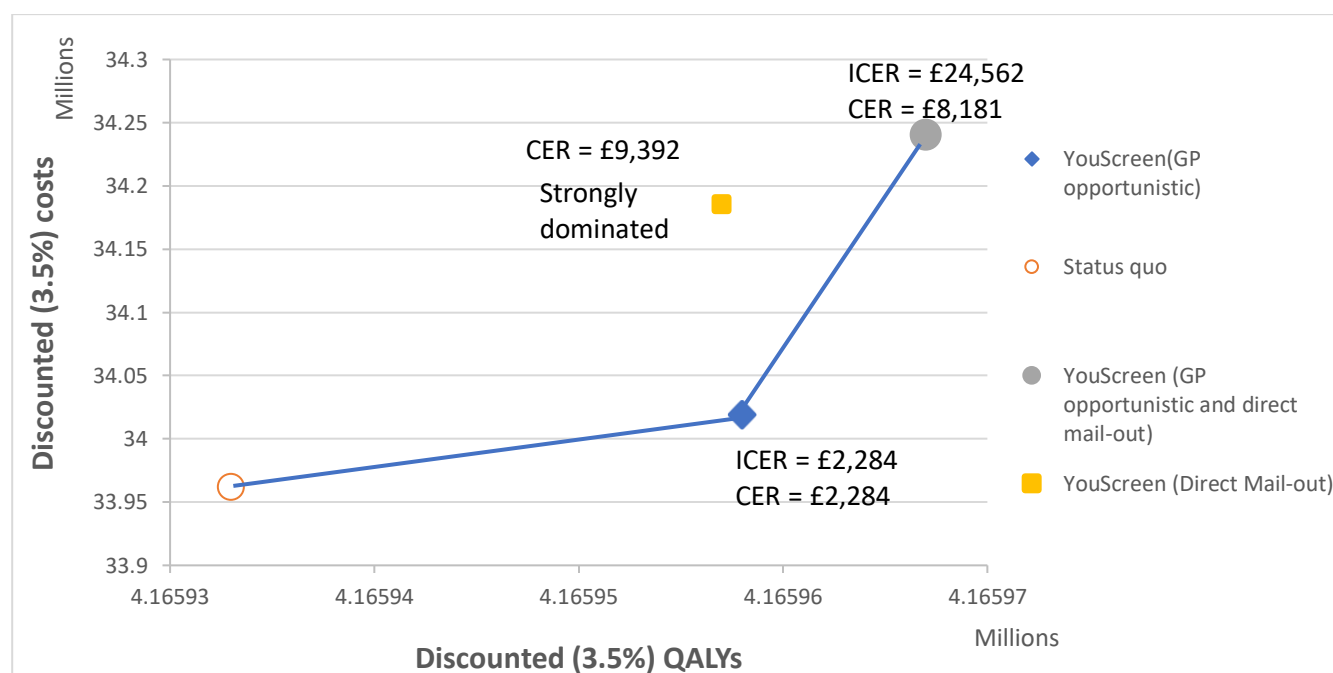
Scenarios	Screening coverage
No YouScreen	68.12% 66.6% 25 – 49 years 70.8% 50 – 64 years
YouScreen direct mail-out:	72.76% 69.8% 25-49 years 77.7% 50-64 years
YouScreen (GP opportunistic):	72.96% 70.0% 25-49 years 77.9% 50-64 years
YouScreen (combined mail-out and GP opportunistic)	74.35% 71.5% 25 – 49 years 79.1% 50 – 64 years

Cost-effectiveness

The primary outcome of this analysis is the comparison between the YouScreen scenarios and the No YouScreen (status quo) scenario. Alongside these results, we present findings from a counterfactual scenario which assumes that no cervical screening is offered at all; this scenario is included for context only, to demonstrate the relative impact that a self-sampling offer may have on health outcomes. When we calculate an incremental cost-effectiveness ratio, we consider “No YouScreen”, rather than “No Screening” as the primary comparator.

We found that offering self-sampling to never- and under-screened women as per the YouScreen (GP opportunistic) pathway would be cost-effective for a cohort of unvaccinated women (ICER = £2,284 per additional QALY gained). Self-sampling under the YouScreen (direct mail-out) pathway was also effective and cost-effective relative to the status quo of screening without self-sampling (cost-effectiveness ratio of £9,392 per additional QALY gained relative to the status quo of screening without self-sampling); however direct mail-out on its own was predicted to be both somewhat less effective and also more costly than the GP opportunistic model. A combined model of GP opportunistic and mail-out was also cost-effective, either compared to YouScreen (GP opportunistic) alone (ICER = £24,562) or to the status quo of screening without self-sampling (CER £8,181). Notably, the ICERs and CERs are subject to input parameters, and in some cases the most cost-effective option is varied in uncertainty analysis (see Figure 12, page 50).

Figure 6 Costs versus quality-adjusted life years (both discounted at 3.5%) for four simulated scenarios over the lifetime of 100,000 women aged 26 at entry. Incremental cost-effectiveness ratios (ICERs) are calculated for scenarios falling along the efficiency frontier (thin line connecting scenarios)⁵



⁵ Any strategy with lower effectiveness but higher costs than another strategy is said to be “strongly dominated”.

Summary of lifetime model findings

Under the 'No YouScreen' scenario assumptions, which involved primary HPV testing at existing coverage levels (approximately 69.6%, from NHS 2022 data), we predict there would be 380 cervical cancer cases, and 119 cervical cancer deaths over the lifetime of a cohort of 100,000 women turning 26 in 2021 (Table 9). The offer of self-sampling under direct mail-out, YouScreen (GP opportunistic), or YouScreen (mail-out and GP opportunistic combined) protocols are predicted to prevent 10 (2.7% relative reduction), 11 (2.9% relative reduction), and 17 (4.5% relative reduction) cervical cancer cases, and 4 (3.0% relative reduction), 4 (3.4% relative reduction), and 4 cervical cancer deaths (3.4% relative reduction), respectively, compared to the No YouScreen scenario.

The direct mail-out offer was predicted to result in 14,432 additional HPV tests, 474 additional colposcopy evaluations, 99 additional precancer treatments, up to £223,892 in additional costs and 24 additional quality-adjusted life-years, relative to the no YouScreen scenario, per 100,000 women. On average, women in the direct mail-out offer scenario received an average of 8.45 HPV tests throughout their lifetime, noting that women with perfect screening attendance (and a negative screening history) will receive 12 HPV tests in their lifetime ³⁸

The YouScreen (GP opportunistic) offer was predicted to result in 15,707 additional HPV tests, 560 additional colposcopy evaluations, 112 additional precancer treatments, up to £57,112 in additional costs and 25 additional quality-adjusted life-years, relative to the no YouScreen scenario, per 100,000 women. On average, women in the YouScreen (GP opportunistic) offer scenario received an average of 8.46 HPV tests throughout their lifetime.

The GP opportunistic and direct mail-out combined arm had a larger impact on screening participation, this scenario was associated with more additional quality adjusted life-years and more additional resources compared to No YouScreen than the YouScreen opportunistic offer, including more HPV tests, colposcopy evaluations, precancer treatments, and costs. Compared to the No YouScreen scenario, the YouScreen (GP opportunistic and direct mail-out) scenario was predicted to result in 28,805 additional HPV tests, 1,074 additional colposcopy evaluations, 221 additional precancer treatments, up to £278,166 in additional costs associated with cervical screening, and 34 additional quality-adjusted life-years, per 100,000 women. In this scenario, women received an average of 8.59 HPV tests in their lifetime.

Table 9 Summary of model findings for a cohort of 100,000 women aged 26 at entry (range includes total range generated by 1-way stochastic uncertainty analysis, excluding alternative cohorts)

Outcome	No Screening	No YouScreen (status quo)	YouScreen (Mail-out)	YouScreen (GP opportunistic)	YouScreen (GP opportunistic + mail-out)
CIN2+ detected	-	5,783	5,856	5,859	5,937
<i>Additional CIN2+ detected</i>	-	-	73	76	154
CIN3+ detected	-	3,711	3,744	3,751	3,788
<i>Additional CIN3+ detected</i>	-	-	33	40	77
Cervical cancer cases	1,316	380	370	369	363
Cervical cancer incidence (ASR)	16.6	4.4	4.3	4.3	4.2

Outcome	No Screening	No YouScreen (status quo)	YouScreen (Mail-out)	YouScreen (GP opportunistic)	YouScreen (GP opportunistic + mail-out)
Cervical cancer cases prevented compared to					
"No Screening"		936	946	947	953
"No YouScreen"	-	-	10	11	17
Cervical cancer deaths	457	119	115	115	115
Cervical cancer mortality (ASR)	5.50	1.31	1.28	1.28	1.26
Cervical cancer deaths prevented compared to:					
"No Screening"	-	338	342	342	342
"No YouScreen"	-	-		4	4
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.38%	0.37%	0.37%	0.36%
Death	0.46%	0.12%	0.12%	0.12%	0.12%
HPV tests	-	830,446	844,878	846,153	859,251
Average lifetime HPV tests per woman	-	8.30	8.45	8.46	8.59
Colposcopy evaluations	-	32,322	32,796	32,882	33,396
Number of colposcopies needed to prevent one cervical cancer case					
compared to "No Screening"	-	34.5	34.7	34.7	35.0
compared to "No YouScreen"	-	-	46.2	50.9	63.2
Number of colposcopies needed to prevent one cervical cancer death					
compared to "No Screening"	-	95.6	96.0	96.1	97.6
compared to "No YouScreen"	-	-	133	140	269
Biopsies	-	24,231	24,556	24,626	24,987
Precancer treatments	-	8,802	8,901	8,914	9,023
Number needed to treat to prevent one cervical cancer case					
compared to "No Screening"	-	9.40	9.41	9.41	9.47
compared to "No YouScreen"	-	-	9.67	10.18	13.00
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	26.04	26.06	26.06	26.38

Outcome	No Screening	No YouScreen (status quo)	YouScreen (Mail-out)	YouScreen (GP opportunistic)	YouScreen (GP opportunistic + mail-out)
<i>compared to "No YouScreen"</i>	-	-	28	28	55
Discounted measurements:					
Total costs	£4,034,224	£33,962,012	£34,185,904	£34,019,124	£34,240,178
Quality-adjusted life-years (QALYs)	4,163,781	4,165,933	4,165,957	4,165,958	4,165,967
Relative to "No Screening"					
Difference in total costs	-	£29,927,788	£30,151,680	£29,984,900	£30,205,954
QALYs gained	-	2,152	2,176	2,177	2,186
CER	-	£13,907	£13,858	£13,773	£13,818
Relative to "No YouScreen"					
Difference in total costs	-	-	£223,892	£57,112	£278,166
QALYs gained	-	-	24	25	34
CER	-	-	£9,392	£2,284	£8,181
Incremental cost per additional:					
CIN2+ detected	-	-	£3,065	£751	£1,806
CIN3+ detected	-	-	£6,715	£1,428	£3,613
Incremental cost-effectiveness ratio (ICER) (per additional QALY gained)	-	-	Strongly dominated**	£2,284	£24,562

* ASR per 100,000 women standardised to the revised 2013 European Standard population. (Office for national statistics 2016).

** Any strategy with lower effectiveness but higher costs than another strategy is said to be "strongly dominated".

Based on model predictions, had self-sampling for under-screened women been operating in England in 2021 (and reached steady state), compared with the status quo scenario without self-sampling, there would have been 2.1% fewer cervical cancer cases and 2.5% fewer cervical cancer deaths in the context of a mail-out offer only; 2.9% fewer cervical cancer cases and 2.6% fewer cervical cancer deaths in the context of a GP opportunistic model; and 5.1% fewer cervical cancer cases and 4.1% fewer cervical cancer deaths in the context of a combined mail-out and GP opportunistic model.

The other health outcomes and resource utilization are summarized in Table 10. We note that the predicted cancer cases and deaths are lower than those observed in 2021 for three reasons. Firstly, because the model predictions reflect outcomes in a cohort offered primary HPV screening since the age of 25 (rather than cytology screening, which was what occurred in reality for many older cohorts). Secondly, because current

relatively high screening coverage rates were used to generate model predictions (as if they had applied for the lifetimes of those in the population), but it had been noted during calibration that it was not possible to reproduce current cervical cancer incidence rates using the current relatively high screening coverage rates (current cervical cancer incidence and related mortality rates would reflect historical patterns of screening in England). And thirdly, because it was thought that national statistics included some misclassification of carcinoma in situ as cancer, whereas this was included in CIN 3 in the model (see *Calibration to England*, page 92).

Table 10 Summary of model findings – results scaled to England female population in 2021*

Outcome	No Screening	No YouScreen (status quo)	YouScreen (Mail-out)	YouScreen (GP opportunistic)	YouScreen (GP opportunistic + direct Mail-out)
CIN2+ detected	-	21,325	21,583	21,597	21,872
<i>Additional CIN2+ detected</i>	-	-	258	272	547
CIN3+ detected	-	13,685	13,799	13,825	13,951
<i>Additional CIN3+ detected</i>	-	-	114	140	266
Cervical cancer cases	4,582	1,263	1,237	1,227	1,198
Cervical cancer cases prevented compared to:					
No Screening	-	3,318	3,345	3,354	3,383
No YouScreen	-	-	26	36	65
Cervical cancer deaths	1,542	380	370	370	364
Cervical cancer deaths prevented compared to:					
No Screening	-	1,162	1,171	1,172	1,178
No YouScreen	-	-	9	10	16
HPV tests	-	3,440,282	3,496,435	3,502,116	3,552,578
Colposcopy evaluations	-	119,874	121,615	121,946	123,842
Biopsies	-	89,927	91,111	91,380	92,705
Precancer treatments	-	32,515	32,865	32,917	33,303

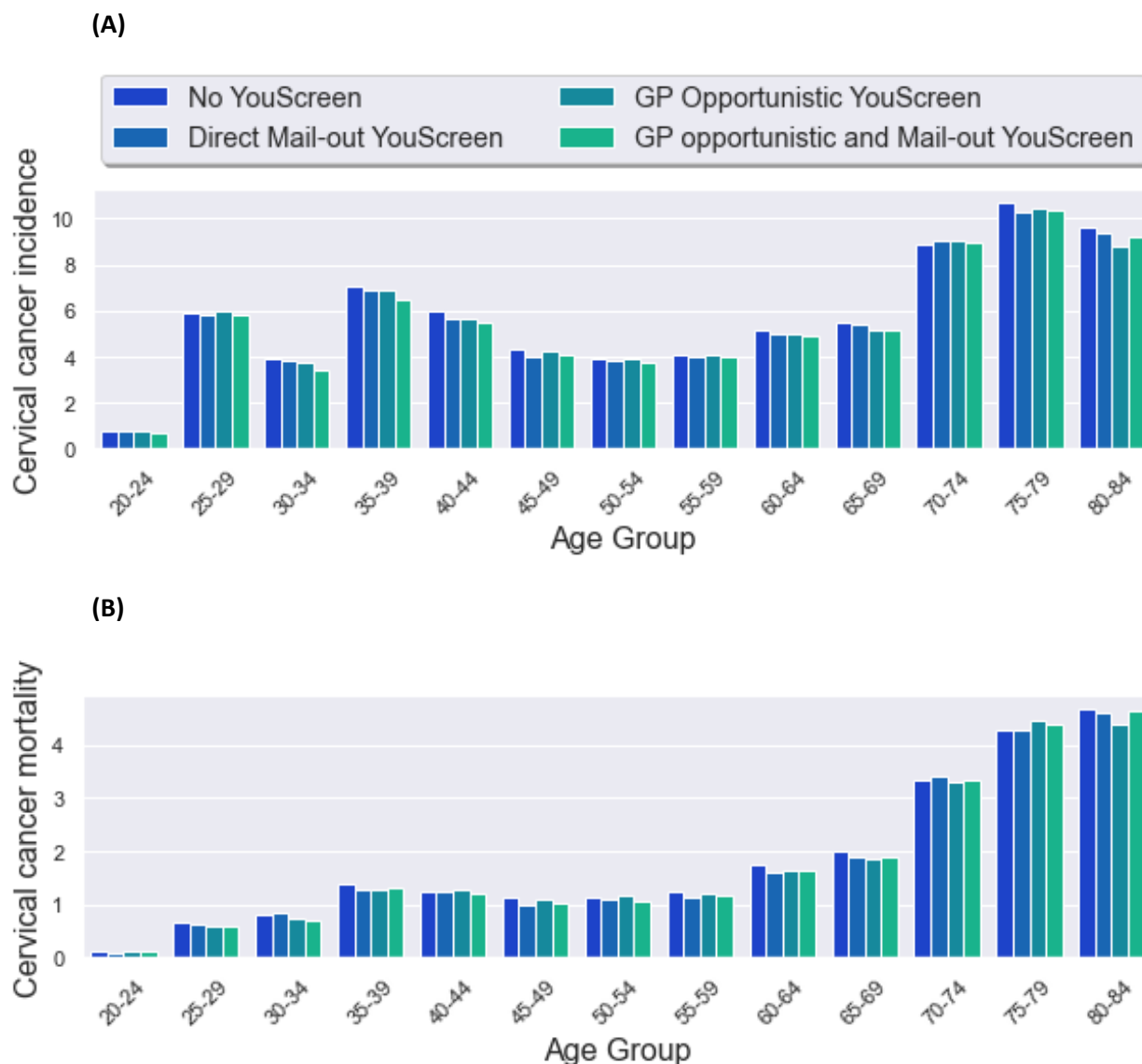
* Age-specific rates from the results over the lifetime of an unvaccinated cohort of women (with or without an offer of self-sampling as per YouScreen from the age of 26) were scaled by the age-specific population size in England in 2021. These represent outcomes which

would have been expected had HPV screening from age 25 (with/ without an offer of self-sampling for under-screened women from age 26) been operating in England in 2021 (and reached steady state).

Cervical cancer incidence and mortality

For all simulated scenarios, cervical cancer incidence rates are predicted to increase or at least maintain at age 25-29, as women initiate cervical screening and prevalent cancers are detected (Figure 7A). Following this, cancer detection rates fall due to the protective effect of sustained HPV testing, before increasing again following screening cessation. Except for ages 25-29, cervical cancer incidence rates were lower in the YouScreen (direct mail-out), YouScreen (GP opportunistic) and YouScreen (direct mail-out and GP opportunistic combined) scenarios than for No YouScreen. We observe similar patterns in cervical cancer mortality among different scenarios. We note the counter-intuitive results for women aged between 70 and 84 regarding cancer incidence and mortality were caused by the stochasticity of the modelling. It is expected that the benefits from YouScreen intervention reduced to negligible 5-10 years after the screening cessation age. So, the effect from the stochasticity can be more easily observed which explains the counter-intuitive cancer incidence and mortality for women aged between 70 and 84.

Figure 7 Predicted age-specific (A) cervical cancer incidence and (B) cervical cancer mortality rates per 100,000 women.

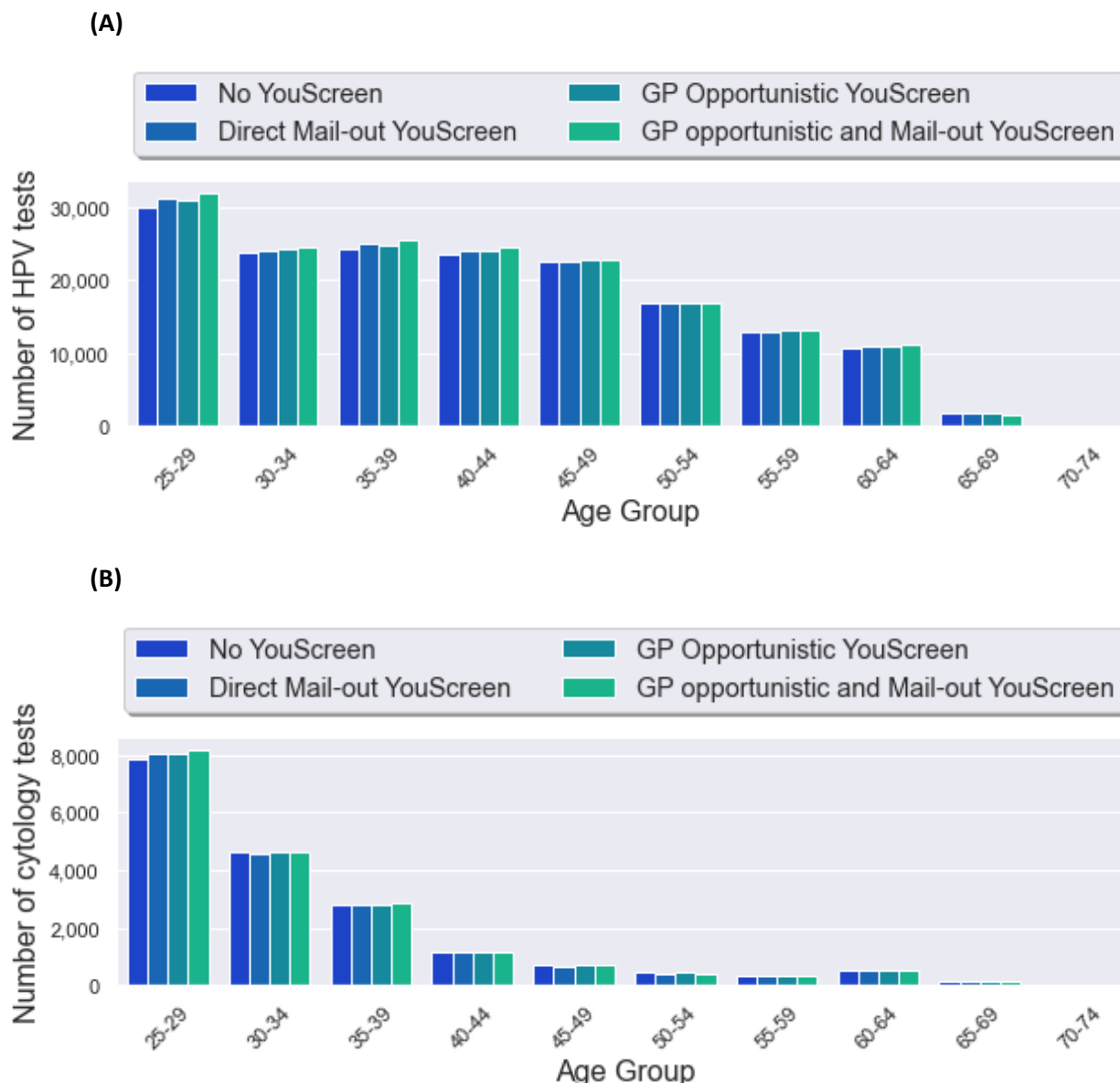


Test volumes and cervical precancer

As expected, for all simulated scenarios the volume of HPV tests increases notably after the screening start age of 25 years and decreases sharply after the recommended end age for screening at age 64 (Figure 8A). A “hard stop” in attendance is not modelled after the screening end-age, due to observed screening participation data indicating that some women are tested beyond the end-age, either due to the completion of recommended follow-up cycles or screening outside of recommendations. Likewise, the number of LBC tests performed are predicted to sharply increase following screening initiation (Figure 8B). Notably, for every 100 HPV tests performed in the 25-29 years age group, 25 liquid-based cytology (LBC) tests are performed, either as a reflex to a positive primary HPV test or as a follow-up test. This number of LBC tests implies, as a proxy, a rate of primary HPV test positivity of approximately 24%. Here, we note that this is a result of several factors including (a) the model is calibrated to age-specific HPV prevalence data (see section 7. Calibration to England) which

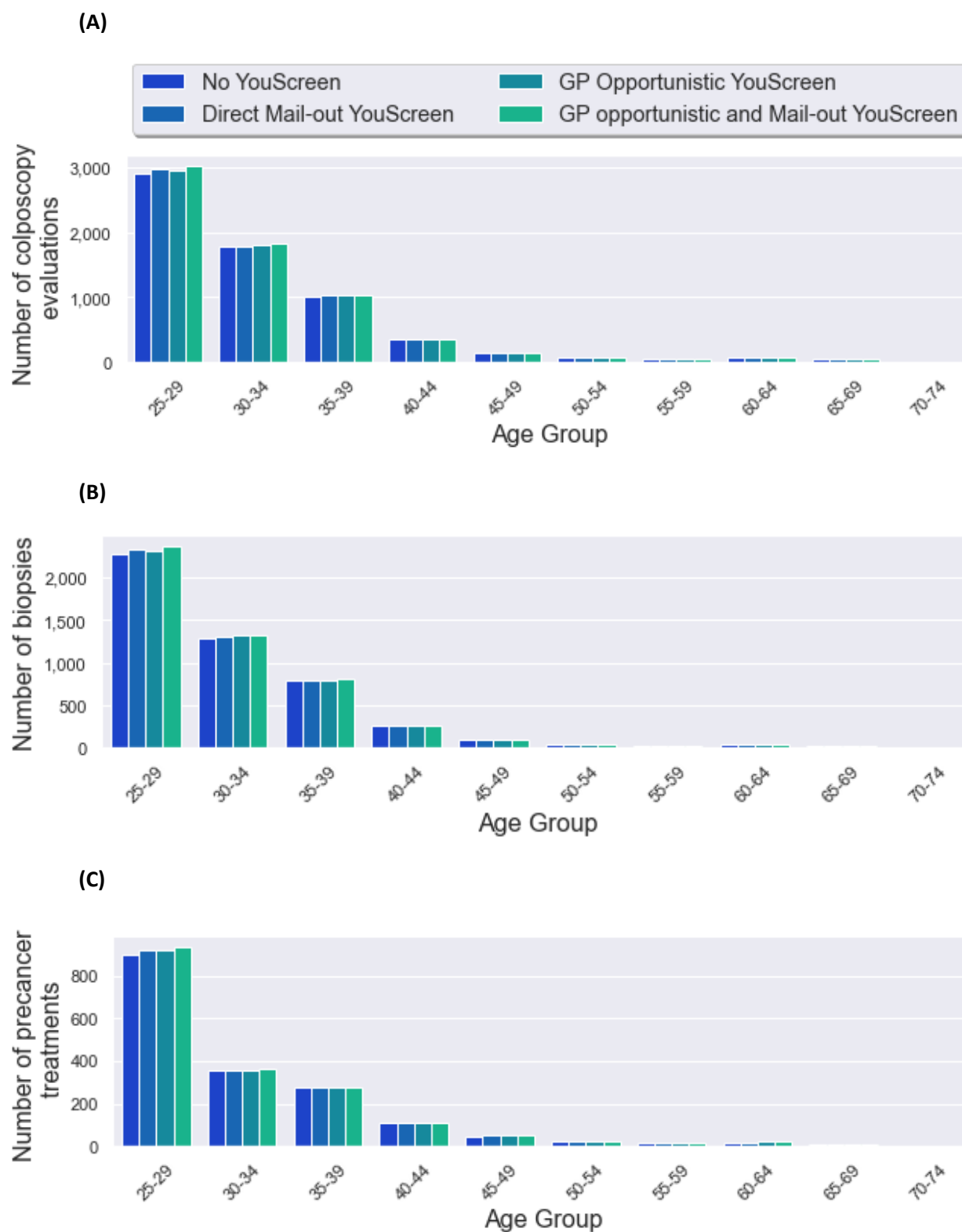
indicates high HPV prevalence in young women, (b) the simulated cohort is an unvaccinated counterfactual to reality, and finally (c) HPV detection in the 25-29 year age group can occur at two separate timepoints within this age-group due to the three-yearly screening interval, and therefore positivity reflects not only prevalent HPV, but also any incident HPV infections which may arise within the interval.

Figure 8 Predicted number of (A) HPV tests and (B) LBC tests by age, per 100,000 women.



Similarly, numbers of colposcopy evaluations, biopsies, and precancer treatments are predicted to increase in YouScreen scenarios compared to No YouScreen, especially for women aged between 25 and 34.

Figure 9 Predicted number of (A) colposcopy evaluations, (B) biopsies, and (C) precancer treatments by age, per 100,000 women.



Uncertainty and sensitivity analyses

One-way stochastic uncertainty analysis

We performed an extensive set of univariate uncertainty analysis to assess the possible impact of a range of factors on the findings of this analysis. The full list and description of each area of uncertainty are described in Table 6 (page 29).

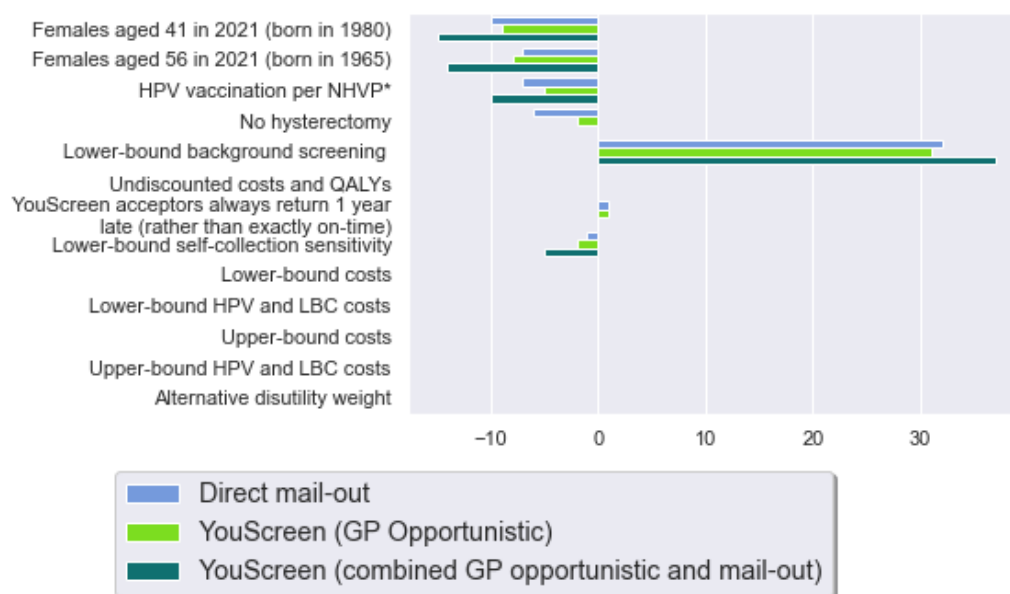
Model predicted cervical cancer cases (Figure 10A) and deaths (Figure 10B) prevented by the YouScreen scenarios are most sensitive to assumptions about background screening coverage; also relatively sensitive to the presence of HPV vaccination and the birth cohort considered; and to a lesser extent, the relative sensitivity of HPV testing on a self-collected versus clinician-collected sample.

1. Offering self-sampling under YouScreen to older cohorts of women (turning 41 or 56 years in 2021) prevented fewer cervical cancer cases and deaths (over their lifetimes) than in the baseline cohort (turning 26 in 2021) due to the shorter time-period in which women are receiving regular screening with self-sampling (around 24 or 9 years, compared to around 39 years).
2. HPV vaccination also reduced the number of cervical cancer cases and deaths prevented, as HPV vaccination lessened the pool of remaining cancers to prevent.
3. Assuming lower rates of background screening participation (equivalent to a number of boroughs in England) increased the number of women offered (and who subsequently accepted) self-sampling under YouScreen, which in turn resulted in more cervical cancer cases and deaths prevented.

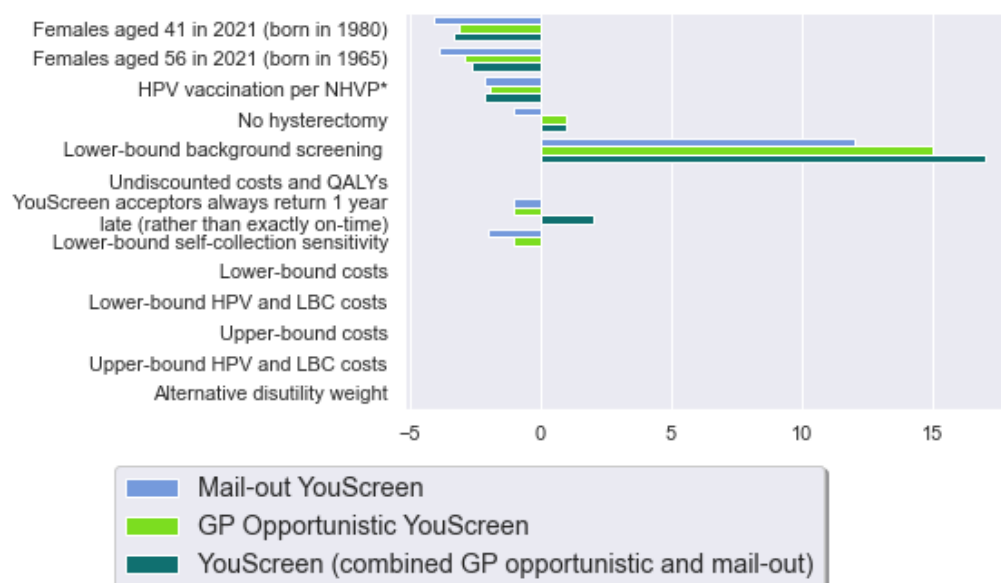
This demonstrates the importance of self-sampling strategies, such as YouScreen, for saving lives in population subgroups who are particularly under-screened, especially if they are also less likely to be vaccinated.

Figure 10 Variation in cervical cancer (A) cases and (B) deaths prevented (compared to No YouScreen)[†] for three self-sampling scenarios, compared to cancer cases and deaths prevented in the baseline analysis, due to variation in a range of parameters*.

(A) cervical cancer cases prevented by self-sampling (compared to No YouScreen) in the sensitivity analysis versus the baseline analysis



(B) cervical cancer deaths prevented by self-sampling (compared to No YouScreen) in the sensitivity analysis versus the baseline analysis



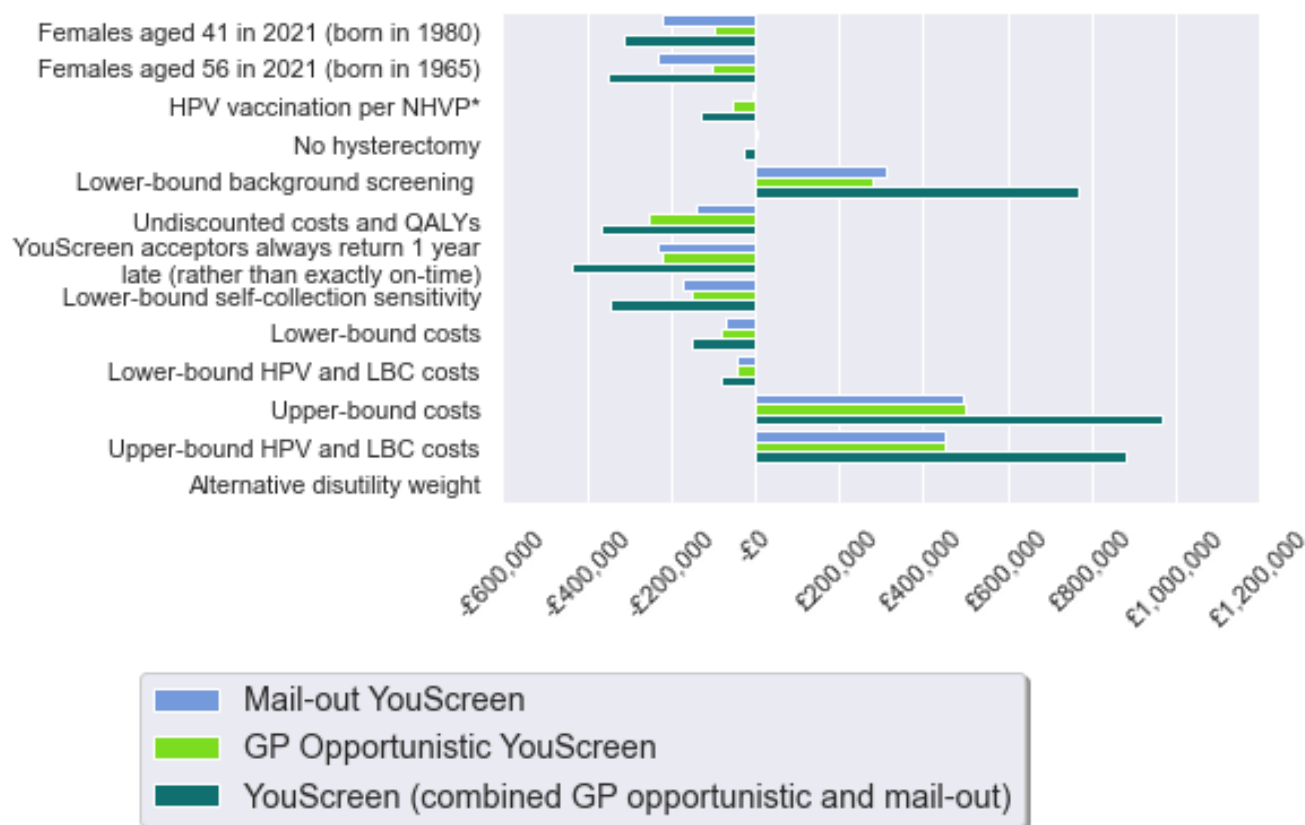
Zero difference in the figure above represents that the number of cases/ deaths prevented by the YouScreen (vs No YouScreen) scenario is the same as it was in the baseline analysis

† cervical cancer cases and deaths per 100,000 women who enter screening when aged 25

* See Table 6 for uncertainty analysis scenarios and description.

Net programme costs per 100,000 women, relative to No YouScreen, were lower for the birth cohorts turning 41 and 56 years in 2021, again because the offer and acceptance of YouScreen (and consequent additional costs) occur later in life (Figure 11). Costs were also lower if those who screened using self-sampling are assumed to continue to attend one year late (rather than on time) or if the relative test sensitivity of self-collected HPV tests was lower and delaying re-screening eligibility in women managed under YouScreen protocols. **Findings are highly sensitive to test cost assumptions**, with the upper bound cost of YouScreen costing up to an extra £10 per woman.

Figure 11 Variation in additional total programme costs† associated with three self-sampling scenarios (compared to the No YouScreen scenario), due to variation in a range of parameters*.



Zero difference in costs in the figure above represents that the difference in costs between the YouScreen and No YouScreen scenarios is the same as it was in the baseline analysis

† costs are discounted, and per 100,000 women who enter screening when aged 25

* The difference in costs between direct mail-out and the No YouScreen scenario is slightly smaller than the difference in baseline analysis.

** See Table 6 for uncertainty analysis scenarios and description.

The discounted cost per additional QALY gained (cost-effectiveness ratio) relative to No YouScreen was sensitive to assumptions explored in sensitivity analysis, and in most cases became more favourable under alternative assumptions compared to the baseline cost-effectiveness ratios (CER) for **a cohort of unvaccinated women** turning 26 in 2021 (Figure 12).

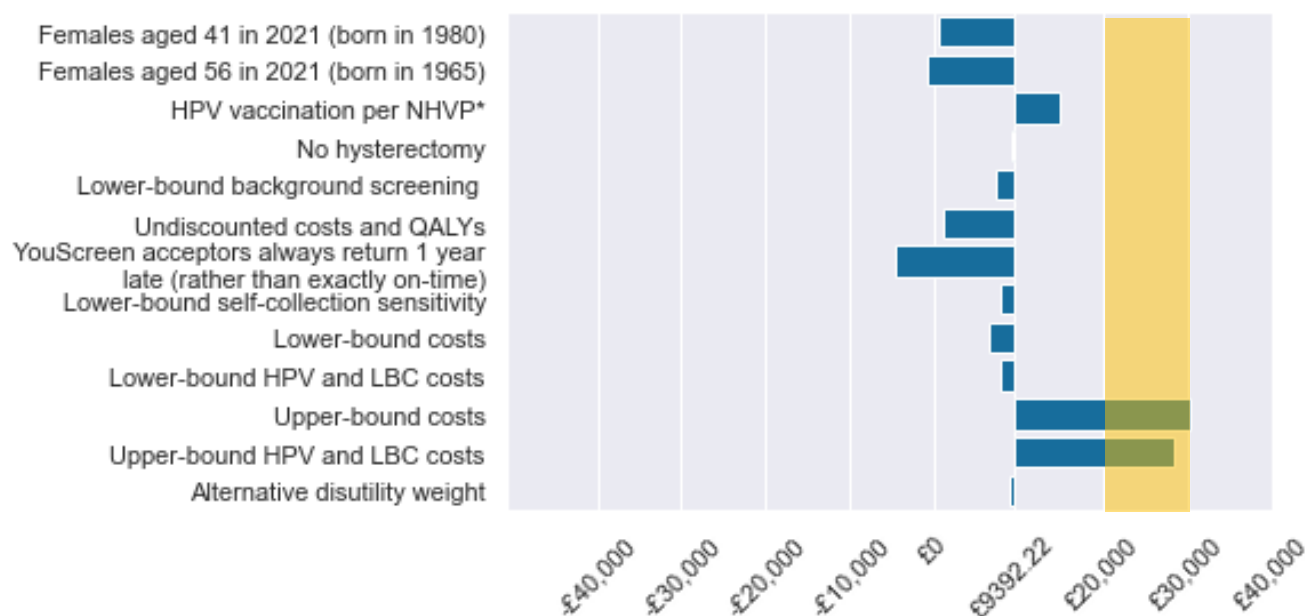
All three self-sampling scenarios were comparatively more cost-effective for the two older cohorts considered (particular for women turning 41 in 2021, born in 1980). The more favourable cost-effectiveness is observed to be from the decreased cost, due to less self-samplings available for older cohorts. When the relative sensitivity of HPV testing on self-samples was assumed to be lower, we also observe more favourable cost-effectiveness. This is mainly due to 1) the attendance of self-sampling in the model was assumed to be perfect attendance, 2) relative lower sensitivity of HPV testing on self-samples will incur less follow-up tests and treatments, hence less costly, and 3) a combination of 1) and 2) implies very effective and sufficient screenings and follow up treatments even lower sensitivity of HPV self-sampling tests was assumed.

Additionally, when HPV test costs were lower, and when under-screened people who used self-sampling were assumed to always return 12 months late for cervical screening (i.e., four-yearly when aged <50 and six-yearly when aged ≥50 years) instead of having perfect on-time adherence to cervical screening (i.e., three-yearly

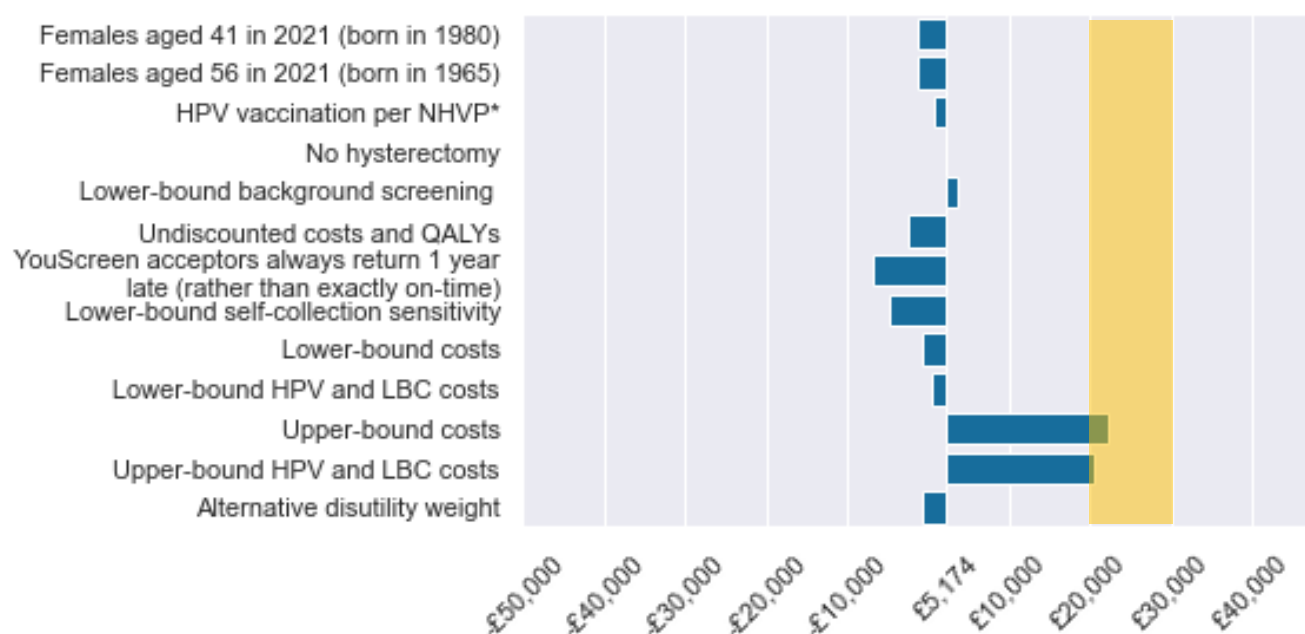
when aged <50 and five-yearly when aged ≥50 years). The exceptions, when cost-effectiveness was less favourable, was in the context of the upper end HPV test cost assumptions (which assumed a higher laboratory cost for self-sampling scenarios). We observe the alternative disutility weights (which assumed a small disutility associated with being screened and a smaller disutility than in the baseline weights for abnormal test results and local or regional cancer) does not substantially impact the incremental cost-effectiveness ratios (ICER). Offering self-sampling opportunistically through GP visits only or mail-out only remained cost-effective at an ICER threshold of £30,000/QALY under all alternative assumptions considered, but the ICER exceeded £30,000 per additional QALY gained in the combined GP opportunistic and mail-out scenario when the laboratory costs for HPV testing increased by £12.91 (from £16.09 to £29.00) and also when all costs (not only HPV test costs) were additionally assumed to be at the upper bound of costs. For the combined scenario, the ICER also exceeded £30,000 per additional QALY gained in the context of the sensitivity analysis for hysterectomy rates (under the extreme assumption that there are no benign hysterectomies performed; Table 19).

Figure 12 Variation in the cost-effectiveness ratio for (A) Direct mail-out only, (B) YouScreen (GP opportunistic only), and (C) YouScreen (GP opportunistic and mail-out combined) scenarios relative to baseline scenario (No YouScreen), due to variation in a range of parameters.

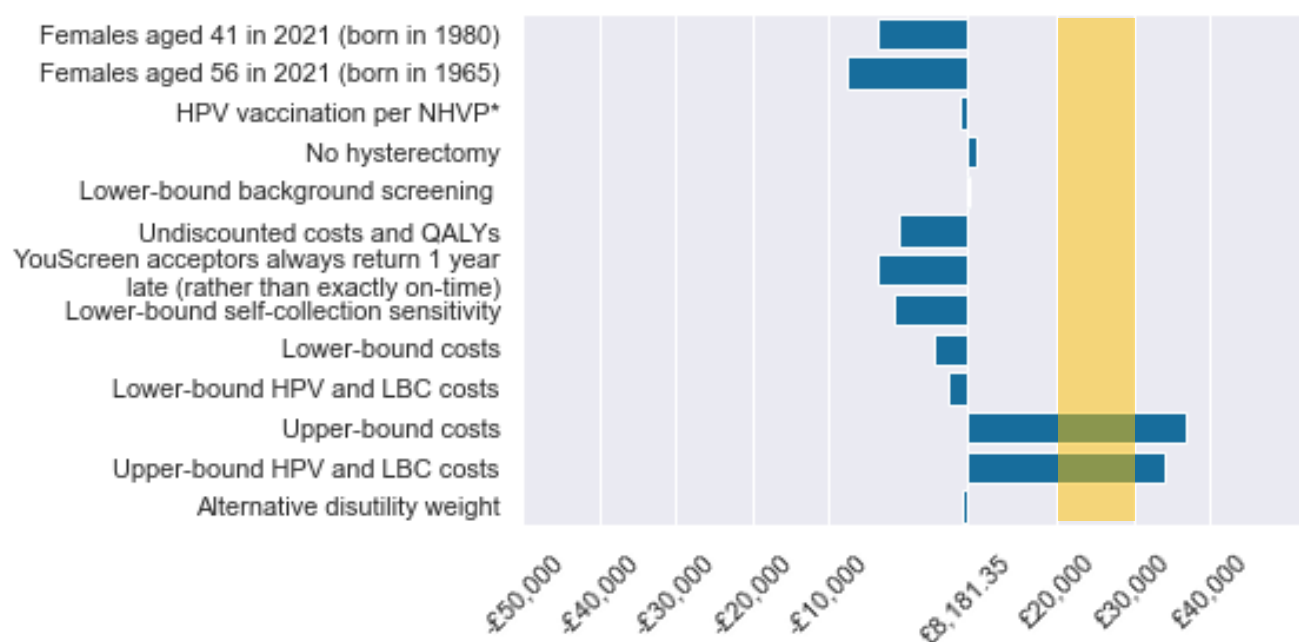
(A) Cost-effectiveness ratio for the direct mail-out scenario relative to the No YouScreen scenario



(B) Cost-effectiveness ratio for the YouScreen (GP opportunistic) scenario relative to the No YouScreen scenario



(C) Cost-effectiveness ratio for the YouScreen (combined GP opportunistic and mail-out) scenario relative to the No YouScreen scenario



Horizontal axis represents the discounted cost (£) per additional QALY gained. The central vertical axis represents the baseline result. Bars appearing to the left of the baseline result indicate that the cost-effectiveness of the scenario is more favourable under the alternative assumptions than under the baseline assumptions, and conversely those appearing on the right are less cost-effective under the alternative assumptions than under the baseline assumptions. The highlighted section (gold) indicates the indicative willingness-to-pay ratio of £20,000-£30,000 per additional QALY gained.

Probabilistic sensitivity analysis

Table 11 reports the discounted costs and QALYs from the PSA for the four screening scenarios and shows the same pattern as with the base case results. The No YouScreen scenario is associated with the lowest costs (£33,312,617; 95% CI: £31,332,945, £35,417,243) and lowest total QALYs (4,166,035; 95% CI: 4,165,941, 4,166,108). YouScreen (direct mail-out) is dominated by YouScreen (GP opportunistic), as YouScreen (GP opportunistic) has more QALYs (4,166,062; 95% CI: 4,165,966, 4,166,136) and lower costs (£33,328,643; 95% CI: £31,329,657, £35,431,376) compared to YouScreen (direct mail-out), which has a total cost of £33,500,486 (95% CI: £31,508,025, £35,709,223) and total QALYs of 4,166,060 (95% CI: 4,165,965, 4,166,135). The YouScreen (combined GP opportunistic and mail-out) scenario achieved the most QALYs 4,166,072 (4,165,976, 4,166,149) but also incurred the highest cost (£33,543,160; 95% CI: £31,559,636, £35,768,058).

Although the relative relationships between the YouScreen scenarios are maintained for the mean costs and QALYs, the costs and QALYs exhibit closely overlapping ranges, leading to overlap on the cost-effectiveness plane (Figure 13). The expected outcomes on the scatter plot show an identical trend as the base case results: (i) the status quo has the lowest expected cost and QALY; (ii) YouScreen (GP opportunistic) dominates YouScreen (Direct mail-out) having a higher QALY gain and a lower cost; and (iii) YouScreen (combined GP opportunistic and mail-out) has the highest costs and QALYs. A significant proportion of simulations overlap across scenarios due to minimal differences in costs and QALYs.

Table 11 PSA results: Mean total Costs, QALYs and ICER and associated 95% CI (per 100,000 women who entered screening when 25; offered YouScreen self-sampling from age 26).

Intervention	Discounted costs (95% CI)	Discounted QALYs (95% CI)	ICER (95% CI)
No YouScreen	£33,312,617 (£31,332,945, £35,417,243)	4,166,035 (4,165,941, 4,166,108)	-
YouScreen (direct mail-out)	£33,500,486 (£31,508,025, £35,709,223)	4,166,060 (4,165,965, 4,166,135)	Dominated
YouScreen (GP opportunistic)	£33,328,643 (£31,329,657, £35,431,376)	4,166,062 (4,165,966, 4,166,136)	£597 (£-95,692, £97,088)
YouScreen (combined GP opportunistic and mail-out)	£33,543,160 (£31,559,636, £35,768,058)	4,166,072 (4,165,976, 4,166,149)	£19,580 (£-217,359, £279,341)

Note: 1. The ICER is compared to the last most effective and non-dominated strategy, i.e., YouScreen (GP opportunistic) has an ICER of £597 compared to No YouScreen; and YouScreen (combined GP opportunistic & mail-out) has an ICER of £19,580 compared to YouScreen (GP opportunistic). 2. Values in this table are rounded.

Figure 13 Cost-effectiveness Plane: lifetime costs versus QALYs (discounted at 3.5% pa), over the lifetime of 100,000 women who entered screening when 25, and YouScreen self-sampling started being offered when they were aged 26.

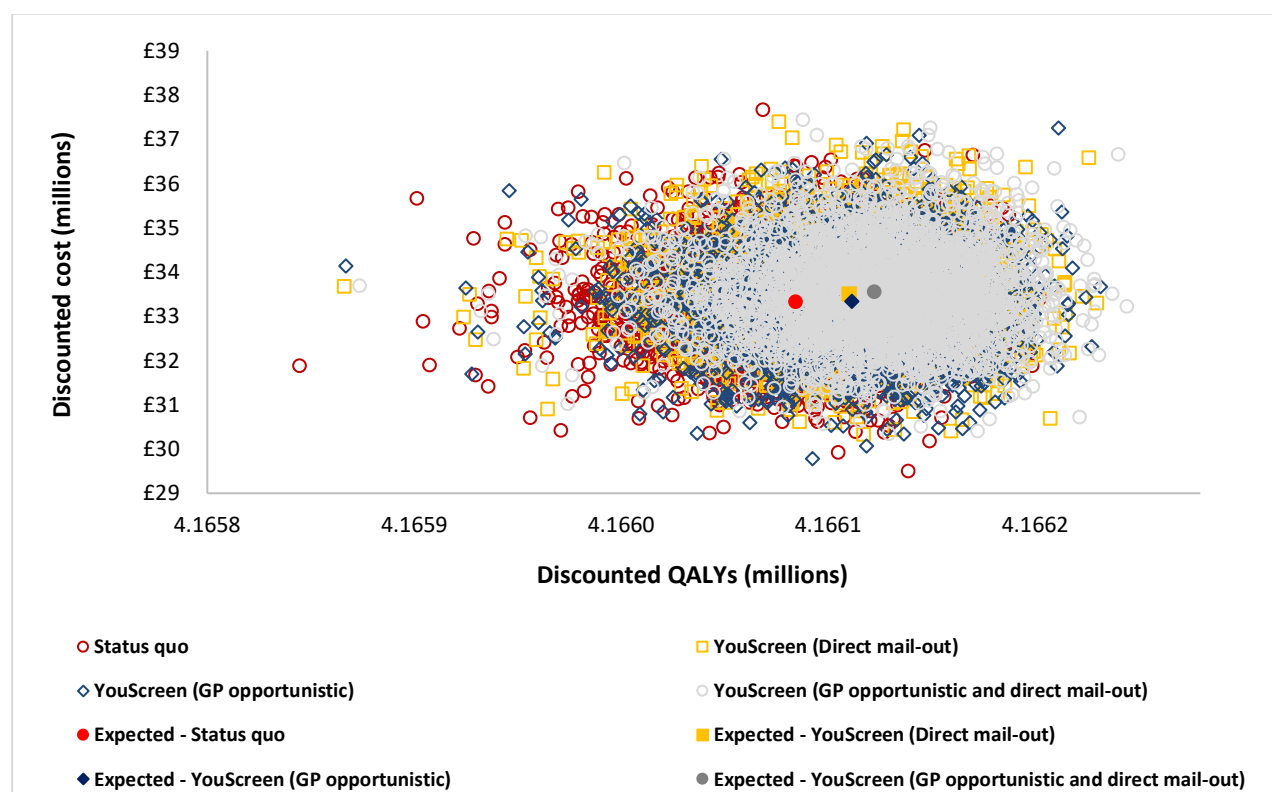


Table 12 shows the cost-effectiveness of the YouScreen scenarios. YouScreen (GP opportunistic) is expected to have a mean additional cost of £16,026 and produce a mean additional 27 QALYs compared to No YouScreen, resulting in an ICER of £597 (95% CI: £-95,692, £97,088). YouScreen (combined GP opportunistic and mail-out) is expected to have a mean additional cost of £214,517 and produce a mean additional 10 QALYs compared to YouScreen (GP Opportunistic), having an ICER of £19,580 (95% CI: £-217,359, £279,341).

YouScreen (combined GP opportunistic and mail-out) has the highest Net Monetary Benefit (NMB) at both the £20,000 and £30,000 WTP threshold (please see Table 12), indicating it is expected to be the most cost-effective scenario at those WTP thresholds. However, these results are uncertain, because the probability of this combined strategy being cost-effective at the £20,000 and £30,000 threshold is 0.421 and 0.474, respectively, with corresponding error probabilities of 0.579 and 0.526 (and because the error probability is greater than 0.5, the decision based on the expected cost-effectiveness is uncertain). The uncertainty is primarily between YouScreen (combined GP opportunistic and mail-out), YouScreen (GP Opportunistic) and No YouScreen. YouScreen (GP Opportunistic) has the second highest chance of being cost-effective (0.381 and 0.389) followed by No YouScreen (0.198 and 0.137), while YouScreen (direct mail-out) is unlikely to be cost-effective at either threshold (probability of being cost-effective was zero).

These findings could also be interpreted as there being reasonably high certainty that a strategy involving an opportunistic GP offer would be cost-effective (0.802 at WTP £20,000 per QALY; 0.863 at WTP £30,000 per QALY), but less certain whether a GP opportunistic offer should be used on its own or in combination with direct mail-out.

Table 12 PSA results: cost-effectiveness and uncertainty.

Intervention	ICER (95% CI)	Threshold = £20,000			Threshold = £30,000		
		NMB (95% CI)	Prob	P (error)	NMB (95% CI)	Prob	P (error)
No YouScreen	-	£83,287,381,154 (£83,284,694,042, £83,289,904,632)	0.198		£124,947,728,039 (£124,944,398,901, £124,950,776,817)	0.137	
YouScreen (direct mail-out)	Dominated	£83,287,704,433 (£83,284,863,825, £83,290,251,740)	0.000		£124,948,306,893 (£124,944,768,261, £124,951,332,164)	0.000	
YouScreen (GP opportunistic)	£597 (£-95,692, £97,088)	£83,287,901,668 (£83,285,116,433, £83,290,470,180)	0.381		£124,948,516,824 (£124,944,988,306, £124,951,631,689)	0.389	
YouScreen (combined GP opportunistic & mail-out)	£19,580 (£-217,359, £279,341)	£83,287,906,272 (£83,285,008,802, £83,290,482,373)	0.421	0.579	£124,948,630,989 (£124,945,047,524, £124,951,728,024)	0.474	0.526

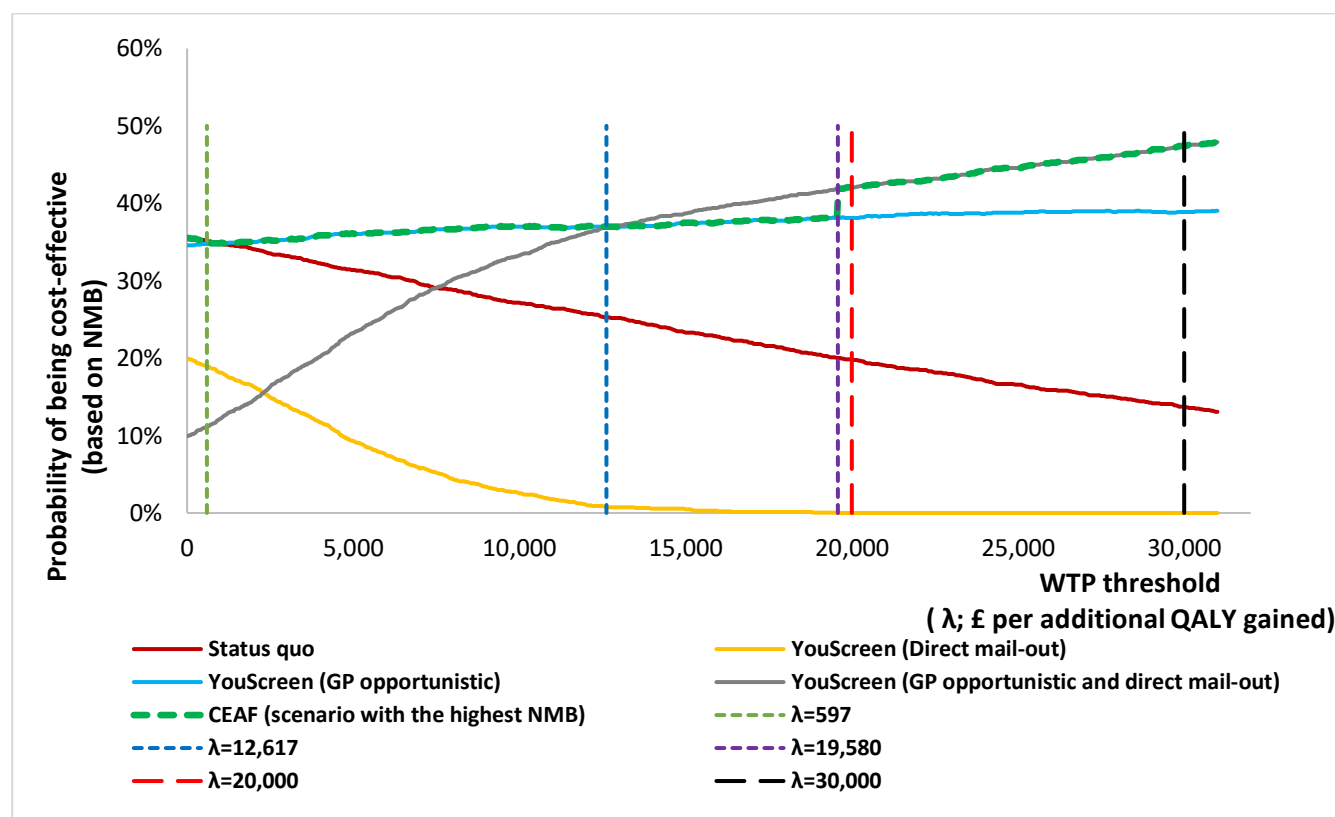
Abbreviation: CI, confidence interval; ICER, incremental cost-effectiveness ratio; NMB, net monetary benefit; Prob, probability of being cost-effective based on the number of times each scenario has the highest NMB in 3,000 simulations; P (error), error probability, calculated as 1 - Prob.

Note: the ICER is compared to the last most effective and non-dominated strategy, i.e., YouScreen (GP opportunistic) has an ICER of £597 compared to No YouScreen; and YouScreen (combined GP opportunistic & mail-out) has an ICER of £19,580 compared to YouScreen (GP opportunistic).

Figure 14 presents the Cost-effectiveness Acceptability Curve (CEAC) and Cost-effectiveness Acceptability Frontier (CEAF). As the WTP threshold increases from zero to £30,000 per additional QALY gained, the probabilities of the YouScreen (GP Opportunistic) and YouScreen (combined GP opportunistic and mail-out)) scenarios being cost-effective increase from 0.346 to 0.389 and from 0.099 to 0.474, respectively (and the combined probability that one of the two strategies involving an opportunistic GP offer is cost-effective increases from 0.445 to 0.863). In contrast, the probability of being cost-effective progressively decreases for the No YouScreen and YouScreen (Mail-out) scenarios, from 0.355 to 0.137 and from 0.200 to 0.000, respectively.

In the PSA, the most cost-effective option varies with the WTP threshold changing as illustrated by CEAF. The status quo (No YouScreen) is the most cost-effective if the WTP threshold is below £597 per additional QALY gained. For a threshold between £597 and £19,580 per additional QALY gained, YouScreen (GP Opportunistic) is the most cost-effective scenario, having the highest mean NMB. Note that the YouScreen (GP Opportunistic) remains the most cost-effective strategy when the WTP threshold is between £12,617 and £19,580 per additional QALY gained, even though YouScreen (combined GP opportunistic and mail-out) has the highest probability of being cost-effective. This is because of the higher mean NMB of YouScreen (GP Opportunistic) in this WTP threshold range. YouScreen (combined GP opportunistic and mail-out) only outweighs YouScreen (GP Opportunistic) to be most cost-effective when the threshold exceeds £19,580 per additional QALY gained.

Figure 14 Cost-effectiveness Acceptability Curve (CEAC) and Cost-effectiveness Acceptability Frontier (CEAF).



Note: 1. CEAC is based on the percentage of simulated times the scenarios have the highest NMB. 2. CEAF is based on the strategy with the highest mean net monetary benefit (NMB)

Discussion

This report provides an assessment of the health, resource-use, and cost implications of routinely offering self-sampling under the YouScreen trial to non-attenders in England. We undertook the analysis in two stages. The first stage of modelling estimated short-term outcomes (over 5 years) of an intervention offered in 2021 (based on the YouScreen protocol), to compare with the trial and project short-term cross-sectional results from the five London boroughs where YouScreen was conducted. This approach incorporates all age groups that are affected by the intervention, allowing for validation against observed trial data (and so may be easier to interpret) and can help to understand the change of the screening coverage at a population level during the years that the YouScreen trial occurred. The limitation of the first stage is the benefits and costs that occur after five years (in particular the impact on cancer cases and deaths, which take longer to accrue) are not taken into account. The second stage of modelling evaluated long-term outcomes and cost-effectiveness, by estimating lifetime outcomes in various single birth cohorts offered self-sampling at different ages. This approach enables the trial results to be extended to the whole population, but with a number of additional assumptions about lifetime screening behaviour over multiple rounds which are not directly obtained from the trial. The two-stage modelling helps to create a comprehensive view of a given medical intervention, is easy to interpret and validate, as well as enabling long-term predictions (given additional conditions).

In the first stage of modelling, it was predicted that all three YouScreen scenarios (direct mail-out, GP opportunistic only, and a combined approach of both that reflected YouScreen as it occurred) would increase the number of women in those boroughs who were screened at least once over the 5-year timeframe by 2.94%, 4.22%, and 6.81%, respectively. It was also shown that all three approaches (direct mail-out, GP opportunistic only, combined approach) would increase CIN2+ (and CIN3+) detection by 8.51% (7.02%), 10.56% (9.65%), and 17.70% (15.40%), respectively. The 5-year timeframe was too short to see a noticeable impact on cancer cases or deaths (apart from a small shift to earlier detection of some cancer cases). Compared to No YouScreen (status quo), the total (discounted) costs over the 5-year period were predicted to be higher for all three scenarios: 4.05% higher for the direct mail-out only scenario, 4.66% higher for the GP opportunistic scenario, and 8.22% higher for the combined approach (YouScreen as it occurred) scenario.

The second stage of modelling evaluated cost-effectiveness by estimating lifetime outcomes of an unvaccinated cohort of 100,000 women who turned 26 in 2021 (notionally born in 1995) over the course of their lifetime considering four screening scenarios: No YouScreen (i.e., current practice), YouScreen (direct mail-out only), YouScreen (GP opportunistic only), YouScreen (combined GP opportunistic and mail-out), and a counterfactual No Screening scenario which was simulated to characterise the burden of disease without any intervention. Compared to the No YouScreen scenario, which represents current practice in England, offering self-sampling to under-screened women nationally via a direct mail-out, opportunistic GP offer, or combination of both was found to prevent 10, 11, and 17 cervical cancer cases, respectively over the lifetime of 100,000 unvaccinated women turning 26 in 2021 (corresponding to relative reductions of 2.7%, 2.9%, and 4.5%, respectively). This corresponds to reductions, which will be realised in very long term for women who screened accordingly, in cervical cancer incidence rates per 100,000 women from 4.4 (no YouScreen) to 4.3, 4.3, and 4.2, respectively, in the simulated cohort while minimally increasing the per-woman average number of lifetime HPV tests from 8.30 to 8.45, 8.46, and 8.59, respectively. Relative to no screening, over the lifetime of cohort,

the number of colposcopies required to prevent one cervical cancer death for the self-sampling scenarios (96.0, 96.1 and 97.6 for direct mail-out, GP opportunistic, and the combined approach, respectively) was similar to that for the existing programme without YouScreen (95.6). The number needed to treat for precancer to prevent one cervical cancer death, relative to no screening, was also very similar for the existing programme (26.0) and the three self-sampling approaches (26.1-26.4). Therefore, all three options for incorporating self-sampling for under-screened women have a balance of benefits and harms that is very similar to the existing programme in England (in addition to being more effective).

Assuming overall HPV test cost (including laboratory delivery costs) of £38.80, £25.51 and £19.65 for clinician-collected, direct mail-out, YouScreen (GP opportunistic) respectively, we found that offering self-sampling to non-attenders as per the YouScreen (GP opportunistic) pathway would be cost-effective for a cohort of unvaccinated women (ICER = £2,284 per additional QALY gained; range across all 1-way uncertainty analyses: cost saving with QALYs gained to £22,250 per additional QALY gained; mean ICER estimate from PSA on costs and QALYs only = £597). Self-sampling under the direct mail-out pathway was more effective than the status quo of screening without self-sampling; however, in both the main analysis and PSA across costs and QALY weights only, direct mail-out on its own was predicted to be both somewhat less effective and also more costly than the GP opportunistic model. A combined model of GP opportunistic and mail-out was also effective, and potentially cost-effective, but this was sensitive to HPV test laboratory costs and the willingness to pay threshold (ICER = £24,562 per additional QALY gained; range across all 1-way uncertainty analyses £12,169-£76,828; mean ICER estimate from PSA on costs and QALYs only = £19,580).

These findings of the two stages, were sensitive to some model input assumptions explored in sensitivity analysis, but in most cases, we found that the cost-effectiveness of the self-sampling scenarios was more favourable under the alternative sets of assumptions. Notably, all of the self-sampling scenarios were comparatively more cost-effective for cohorts who were older in 2021 (aged 41 or 56) than for the baseline cohort of unvaccinated women turning 26 in 2021, and also cost-saving (while also improving QALYs overall) relative to the status quo without self-sampling for GP opportunistic only and the combined approach. In some cases, cost-effectiveness was more favourable even though the self-sampling scenarios were less effective under the alternative assumptions than they were under the primary set of assumptions (though always more effective than the scenario with no self-sampling), because this was outweighed by lower costs (including older cohorts, lower sensitivity of self-sampling, slower return for routine screening). Additionally, we found the incremental cost-effectiveness ratios were more favourable when the lower bound cost for self-sampling was assumed. In some situations, the incremental cost-effectiveness ratios were less favourable for the self-sampling scenarios under alternative assumptions, specifically when the upper bound costs were assumed. Nevertheless, even though the incremental cost-effectiveness ratios were less favourable in these two cases, they remained below £30,000 per additional QALY gained for the direct mail-out only and opportunistic GP offer (but not the combined scenario). In contrast, we observed insignificant changes in ratios when an alternative QALY weights set was used (which assigns disutility to a negative screening test to reflect the experience of being screened, but also assigns less disutility to colposcopy referral and treatment of cervical precancer). The direction of these effects is not unexpected: as the self-sampling induces more people to be screened and tests to be done (including more negative test results than the status quo without self-sampling).

Findings from the PSA on costs and QALY weights, which examined the effects of uncertainty in this specific subset of parameters in more detail, supported the main findings that a strategy involving an opportunistic GP offer was likely to be cost-effective, and that whether or not it should be combined with a direct mail-out approach was dependent on the WTP threshold. GP opportunistic alone was the most cost-effective for a WTP

threshold in the range of £597 – 19,580 per additional QALY gained, and a combined approach of an opportunistic GP offer and direct mail-out was the most cost-effective when WTP exceeded £19,580 per additional QALY gained. There was some uncertainty between these two strategies, as the probability of error in finding the combined approach cost-effective at the WTP threshold of £20,000-30,000 per QALY ranges from 0.137 to 0.198. The findings from the partial PSA on costs also assumed that HPV test laboratory costs remained close to the usual unit cost for clinician-collected samples (95% CI of costs explored in PSA: £12.67 - £16.18). This difference in the range of costs explored may explain why the ICER for the combined strategy exceeded £30,000 per QALY in the univariate sensitivity analysis (which assumed a substantially higher laboratory cost of £29, compared £16.09 in the baseline analysis), but not in the partial PSA on costs and QALY weights. This demonstrates the importance of this cost.

HPV vaccination reduced the cost-effectiveness of the direct mail-out scenario, but the cost-effectiveness of the GP opportunistic only or the combined pathway was relatively insensitive to HPV vaccination. This variation is primarily driven by the differing effect of HPV vaccination on the costs (particularly on the delivery related cost) of the three self-sampling scenarios, as all were relatively less effective in the context of vaccination, because the underlying risk of disease was lower. In all three scenarios, HPV vaccination meant that overall costs were more strongly driven by the cost of screening, because follow-up tests and treatments were all reduced by vaccination, but screening costs were relatively unchanged. The screening costs for each scenario in the model is affected by the overall cost of HPV screening including delivery, which differs for clinician-collection, direct mailout, and self-samples collected opportunistically at GP visits, and by number of tests which are self-collected versus clinician-collected (which is affected by uptake of self-sampling, as this shifts some people who would have eventually screened with a clinician-collected test to be screened earlier using self-sampling; see Figure 23 in Appendix 3). The GP opportunistic scenario had higher uptake than the direct mail-out scenario, so had more tests overall, but fewer were clinician-collected tests (as more people had used self-sampling), and in this scenario, the total cost which includes laboratory cost and delivery cost, where the delivery of the clinician-collected tests is substantially more expensive than self-collected tests (£38.80 vs £19.65). In contrast, the lower uptake in the direct mail-out scenario means that a higher proportion of HPV tests overall are the more expensive clinician-collected tests. Additionally, the cost of self-collected tests is relatively high in the direct mail-out scenario: firstly as the total cost of the screen is more expensive than in the GP opportunistic scenario (£25.51 vs £19.65); and secondly because the effective cost is even higher, as approximately 7 to 8 test kits are sent out for each test returned in the first direct mail-out offer (although once people have used self-sampling using direct mail-out, they continue to do so). Over the lifetime of someone who is first offered and uses self-sampling at age 26 (including at every recommended test thereafter), they will have around 11 HPV tests, but a further 7 to 8 kits needed to be sent for their first test to be returned. Effectively, this means that their 11 tests required 18 to 19 kits in total to be sent plus 11 laboratory tests, so the cost of each HPV test in their lifetime was approximately £29 to £32. This contributes to the difference in costs between the direct mail-out scenario and the scenario with no self-sampling being relatively stable regardless of HPV vaccination.

The analysis utilised the *Policy1-Cervix* platform, which incorporates detailed aspects of the national cervical screening programme in England and has an extensively validated HPV natural history. Extensive uncertainty analysis has been performed, which includes alternative assumptions for age when self-sampling for non-attenders is introduced, background screening behaviour (outside of YouScreen), HPV vaccination, self-collected HPV test sensitivity and hysterectomy, and both 1-way and probabilistic sensitivity analyses on costs and disutility assumptions.

In 1-way uncertainty analysis, we found that with age at offer of self-sampling, **HPV vaccination assumptions play an important role in both the expected health benefit and cost-effectiveness of YouScreen intervention scenarios.** Our findings that introducing self-sampling for under-screened women, even at relatively older ages, was found to be both cost saving and increased QALYs overall underscores the importance of a rapid roll-out to capture as many under-screened women as possible. In a cohort of women offered HPV vaccination at high coverage, YouScreen scenarios remained effective compared to the existing screening regimen without self-sampling, with YouScreen (GP opportunistic) being the most cost-effective option under the indicative willingness-to-pay threshold of £20,000-£30,000 (ICER=£707). It is important to note that the existing screening regimen itself will become less cost-effective for vaccinated cohorts (CER compared to no screening £27,523 per additional QALY gained for a cohort offered vaccination in early adolescence, compared to £13,907 per additional QALY gained for unvaccinated cohort). The balance of benefits vs harms will also shift, and therefore less intensive screening is likely to be more appropriate for vaccinated cohorts, based on analyses for England specifically ^{19,38} and similar findings for other settings. It appears possible that some form of self-sampling may be cost-effective for overdue women in vaccinated cohorts, but this has not been fully explored here.

LIMITATIONS

Modelling of this nature is subject to a range of limitations and this analysis is no different. Specific limitations in this analysis are described below.

1. There exists substantial uncertainty surrounding the pre-vaccination underlying HPV infection risk for women in general in England, as noted in the calibration report. In the current analysis, we have prioritised a model fit to cervical screening behaviour rather than current estimates of age-specific cervical cancer incidence (since these reflect past screening patterns more than current screening behaviour). As such, **we may be underestimating the overall risk of HPV disease in women in England - but this would have the subsequent effect of our findings underestimating the effectiveness and cost-effectiveness of the YouScreen protocols.**
2. In this study we have focussed on the modelling of a single cohort, chosen to represent the eventual long-term impact of the HPV primary screening programme without HPV vaccination. However, as the screen-eligible population currently primarily consists of women with a lifetime of screening under primary cytology (which is less effective than HPV screening), this has some limitations. Firstly, it is likely that our findings for older birth cohorts are further underestimating risks of cervical disease in the near-term (but nevertheless found self-sampling would represent very good value for money in older cohorts). Secondly, the estimates that are scaled up to represent England in 2021 would underestimate disease in all screening scenarios (including the No YouScreen scenario), and so potentially also underestimate the absolute benefit from the YouScreen scenarios.
3. There are other factors which may have affected the number of both offers and acceptance of self-sampling under the GP opportunistic trial arm. More specifically, these are the restrictions under which the YouScreen offer could be made, the impact of COVID pandemic on GP workload, and the rejection of self-samples at the laboratory prior to being analysed as a result of missing lab forms, which is not likely to happen in a national programmatic implementation. Therefore, it is likely that the YouScreen trial outcome provides an underestimation of the proportion of women who would accept the self-sampling under a GP opportunistic pathway, with the subsequent consequence of the modelling

underestimating both the impact and cost of the YouScreen (GP opportunistic) and the YouScreen (as it occurred, or mail-out and GP opportunistic combined). In summary, these factors are more likely to impact on the **absolute benefits of the intervention to the population, rather than the cost-effectiveness ratio. The absolute benefit may have been underestimated in this analysis.**

Taking these first three limitations together, **it is likely that extending self-sampling to women who are non-attenders (specifically women who were overdue for screening and previously screened by cytology) in England will be more effective and cost-effective than indicated by the findings of this analysis,** especially in the near-term before the benefits of HPV vaccination have reached fruition given that the oldest routinely vaccinated cohort is due to turn 28 in 2023.¹⁷.

4. Finally, there is extensive uncertainty surrounding the costs of provision of both the primary HPV screening programme, and costs incurred by the possible expansion of self-sampling under YouScreen. Cost outcomes for model results are highly contingent on pricing assumptions for primary HPV tests under various delivery modes. A lower and upper bound of cost assumptions have been considered in one-way uncertainty analysis, with the YouScreen (GP opportunistic) scenario being cost-saving, while mail-out only and a combined approach of mail-out and GP opportunistic offers (as in YouScreen) being cost-effective, compared to No YouScreen, when a lower bound of cost assumption is made. When an upper bound of cost assumption is made, the incremental cost-effectiveness ratios (relative to No YouScreen) become less favourable, with YouScreen (mail-out and GP opportunistic combined) exceeding the indicative willingness-to-pay threshold (Table 21 and Table 22 in *Additional Tables*). The costs associated with self-sampling were based directly on YouScreen, and in some cases these may overestimate costs of delivering more widely - for example, the addition of trial-related documentation to self-sampling kits and trial management added further cost to the YouScreen (direct mail-out) estimates.

Based on the overall findings of this analysis, offering self-sampling to never screened and under-screened women in England across a range of ages as part of the national cervical screening programme, particularly when offered in a GP setting, is both effective and cost-effective. An approach which entirely relies on direct mail-out is predicted to be both more costly and less effective than offering self-sampling in a GP setting, but direct mail-out could potentially supplement a GP-based approach to self-sampling provided test costs are low enough.

Despite the uncertainties, the strengths of the analysis include the use of an extensively calibrated and comprehensive model platform and the direct use of data from an important local study, embedded in the health services context in the UK. The analysis has provided support for the incremental benefits and cost-effectiveness of self-sampling in the UK NHS Cervical Screening Programme.

Additional tables

Table 13 Summary of model findings for a cohort⁶ of 100,000 women turning 41 in 2021.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,205	5,211	5,213	5,214
Additional CIN2+ detected	-	-	6	8	9
CIN3+ detected	-	3,591	3,595	3,598	3,599
Additional CIN3+ detected	-	-	4	7	8
Cervical cancer cases	1318	462	462	460	460
Cervical cancer incidence (ASR)	16.57	5.53	5.53	5.50	5.51
Cervical cancer cases prevented compared to					
“No Screening”	-	856	856	858	858
“No YouScreen”	-	-	0	2	2
Cervical cancer deaths	457	147	147	146	146
Cervical cancer mortality (ASR)	5.53	1.67	1.66	1.66	1.66
Cervical cancer deaths prevented compared to:					
“No Screening”	-	310	310	311	311
“No YouScreen”	-	-	0	1	1
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.46%	0.46%	0.46%	0.46%
Death	0.46%	0.15%	0.15%	0.15%	0.15%
HPV tests	-	453,351	454,050	454,432	455,324
Average lifetime HPV tests per woman	-	4.53	4.54	4.54	4.55
Colposcopy evaluations	-	21,105	21,147	21,150	21,128

⁶ For all the scenario simulations, we simulated a cohort of 100,000 or 10,000,000 women for stability of model estimates, and is not intended to directly relate to a real-life birth cohort.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Number of colposcopies needed to prevent one cervical cancer case					
compared to "No Screening"	-	24.7	24.7	24.7	24.6
compared to "No YouScreen"	-	-	N/A	22.5	11.5
Number of colposcopies needed to prevent one cervical cancer death					
compared to "No Screening"	-	68.1	68.2	68.0	67.9
compared to "No YouScreen"	-	-	999.7	45.0	23.0
Biopsies	0	14,933	14,946	14,962	14,967
Precancer treatments	0	6,103	6,107	6,109	6,113
Number needed to treat to prevent one cervical cancer case					
compared to "No Screening"	-	7.13	7.13	7.12	7.12
compared to "No YouScreen"	-	-	N/A	3.00	5.00
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	19.69	19.70	19.64	19.66
compared to "No YouScreen"	-	-	106	6	10
Discounted measurements:					
Total costs	£6,354,677	£22,906,820	£22,910,163	£22,868,977	£22,874,591
Quality-adjusted life-years (QALYs)	5,334,447	5,337,862	5,337,870	5,337,895	5,337,871
Relative to "No Screening"					
Difference in total costs	-	£16,552,143	£16,555,486	£16,514,300	£16,519,914
QALYs gained	-	3,415	3,423	3,448	3,424
CER	-	£4,847	£4,836	£4,790	£4,825
Relative to "No YouScreen"					
Difference in total costs	-	-	£3,343	-£37,843	-£32,229
QALYs gained	-	-	8	33	9
CER	-	-	£403	-£1,147	-£3,581
Incremental cost per additional:					

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Incremental cost per extra CIN2+ detected	-	-	£557	-£4,730	-£3,581
Incremental cost per extra CIN3+ detected	-	-	£836	-£5,406	-£4,029
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	Strongly dominated	cost saving	cost saving

Table 14 Summary of model findings for a cohort of 100,000 women turning 56 in 2021.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,136	5,136	5,136	5,136
Additional CIN2+ detected	-	-	0*	0*	0*
CIN3+ detected	-	3,554	3,554	3,554	3,554
Additional CIN3+ detected	-	-	0*	0*	0*
Cervical cancer cases	1315	486	483	483	483
Cervical cancer incidence (ASR)	16.52	5.82	5.78	5.78	5.78
Cervical cancer cases prevented compared to:					
“No Screening”	-	829	832	832	832
“No YouScreen”	-	-	3	3	3
Cervical cancer deaths	459	155	155	154	154
Cervical cancer mortality (ASR)	5.56	1.77	1.77	1.74	1.76
Cervical cancer deaths prevented compared to:					
“No Screening”	-	304	304	305	305
“No YouScreen”	-	-	0	1	1
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.49%	0.48%	0.48%	0.48%
Death	0.46%	0.16%	0.16%	0.15%	0.15%

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
HPV tests	-	160,128	160,025	159,988	159,675
Average lifetime HPV tests per woman	-	1.60	1.60	1.60	1.60
Colposcopy evaluations	-	22,319	22,334	22,314	22,306
Number of colposcopies needed to prevent one cervical cancer case					
compared to "No Screening"	-	26.9	26.8	26.8	26.8
compared to "No YouScreen"	-	-	4.84	-1.67	-4.33
Number of colposcopies needed to prevent one cervical cancer death					
compared to "No Screening"	-	73.4	73.5	73.2	73.1
compared to "No YouScreen"	-	-	N/A	-5.00	-13.00
Biopsies	0	15,440	15,442	15,427	15,422
Precancer treatments	0	6,191	6,198	6,196	6,178
Number needed to treat to prevent one cervical cancer case					
compared to "No Screening"	-	7.47	7.45	7.45	7.43
compared to "No YouScreen"	-	-	2.42	1.67	-4.33
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	20.37	20.39	20.31	20.26
compared to "No YouScreen"	-	-	N/A	5	-13
Discounted measurements:					
Total costs	£8,426,698	£15,835,576	£15,827,778	£15,789,068	£15,766,193
Quality-adjusted life-years (QALYs)	5,334,447	5,337,862	5,337,870	5,337,895	5,337,871
Relative to "No Screening"					
Difference in total costs	-	£7,408,878	£7,401,080	£7,362,370	£7,339,495
QALYs gained	-	3,415	3,423	3,448	3,424
CER	-	£2,170	£2,162	£2,135	£2,144
Relative to "No YouScreen":					

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Difference in total costs	-	-	-£7,798	-£46,508	-£69,383
QALYs gained	-	-	8	33	9
CER	-	-	-£941	-£1,409	-£7,709
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	N/A	N/A	N/A
Incremental cost per extra CIN3+ detected	-	-	N/A	N/A	N/A
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	Strongly dominated	cost saving	cost saving

*These numbers are not zero but rounded to 0.

Table 15 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 and who were offered HPV vaccination at age 12⁷.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	3,555	3,600	3,601	3,637
Additional CIN2+ detected	-	-	45	46	82
CIN3+ detected	-	2,204	2,230	2,230	2,244
Additional CIN3+ detected	-	-	26	26	40
Cervical cancer cases	630	201	198	195	194
Cervical cancer incidence (ASR)	7.91	2.34	2.30	2.26	2.25
Cervical cancer cases prevented compared to:					
“No Screening”	-	429	432	435	436
“No YouScreen”	-	-	3	6	7
Cervical cancer deaths	222	64	62	62	62

⁷ Modelled uptake approximately 89% at age 12 years. The assumed HPV vaccination programme coverage (single-dose effective) for catch-up (aged 14-18 years over 2008-2010) and routine cohorts (aged 12/13 in a given school year) is shown in Figure 3 in the section *HPV immunisation programme features and coverage*.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Cervical cancer mortality (ASR)	2.69	0.71	0.68	0.68	0.68
Cervical cancer deaths prevented compared to:					
“No Screening”	-	158	160	160	160
“No YouScreen”	-	-	2	2	2
Cumulative life risk of cervical cancer: diagnosis	0.63%	0.20%	0.20%	0.20%	0.19%
Death	0.22%	0.06%	0.06%	0.06%	0.06%
HPV tests	-	815,825	830,858	831,683	845,034
Average lifetime HPV tests per woman	-	8.16	8.31	8.32	8.45
Colposcopy evaluations	-	21,639	22,111	22,111	22,474
Number of colposcopies needed to prevent one cervical cancer case					
compared to “No Screening”	-	50.4	51.2	50.8	51.5
compared to “No YouScreen”	-	-	157.3	78.7	119.3
Number of colposcopies needed to prevent one cervical cancer death					
compared to “No Screening”	-	137.0	138.2	138.2	140.5
compared to “No YouScreen”	-	-	236.0	236.0	417.5
Biopsies	0	16,118	16,398	16,435	16,667
Precancer treatments	0	5,637	5,692	5,700	5,747
Number needed to treat to prevent one cervical cancer case					
compared to “No Screening”	-	13.14	13.18	13.10	13.18
compared to “No YouScreen”	-	-	18.33	10.50	15.71
Number needed to treat to prevent one cervical cancer death					
compared to “No Screening”	-	35.68	35.58	35.63	35.92
compared to “No YouScreen”	-	-	28	21	37
Discounted measurements:					
Total costs	£1,940,269	£28,803,042	£29,023,518	£28,809,408	£28,955,436

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Quality-adjusted life-years (QALYs)	4,165,331	4,166,307	4,166,322	4,166,316	4,166,328
Relative to "No Screening":					
Difference in total costs	-	£26,862,773	£27,083,249	£26,869,139	£27,015,167
QALYs gained	-	976	991	985	997
CER	-	£27,523	£27,329	£27,278	£27,096
Relative to "No YouScreen"					
Difference in total costs	-	-	£220,476	£6,366	£152,394
QALYs gained	-	-	15	9	16
CER	-	-	£14,698	£707	£7,257
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	£4,863	£137	£1,851
Incremental cost per extra CIN3+ detected	-	-	£8,480	£245	£3,810
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	<i>Dominated</i>	£707	£12,169

Table 16 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when the lower bound of screening participation is assumed.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	4,958	5,189	5,279	5,393
Additional CIN2+ detected	-	-	231	321	435
CIN3+ detected	-	3,430	3,569	3,623	3,655
Additional CIN3+ detected	-	-	139	193	225
Cervical cancer cases	1314	400	358	358	346
Cervical cancer incidence (ASR)	16.50	4.72	4.22	4.22	4.07

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Cervical cancer cases prevented compared to:					
“No Screening”	-	914	956	956	968
“No YouScreen”	-	-	42	42	54
Cervical cancer deaths	456	124	108	105	103
Cervical cancer mortality (ASR)	5.53	1.40	1.22	1.16	1.15
Cervical cancer deaths prevented compared to:					
“No Screening”	-	332	348	351	353
“No YouScreen”	-	-	16	19	21
Cumulative life risk of cervical cancer: diagnosis	1.31%	0.40%	0.36%	0.36%	0.35%
Death	0.46%	0.12%	0.11%	0.11%	0.10%
HPV tests	-	683,795	717,927	737,138	766,189
Average lifetime HPV tests per woman	-	6.84	7.18	7.37	7.66
Colposcopy evaluations	-	25,273	26,749	27,297	28,361
Number of colposcopies needed to prevent one cervical cancer case					
compared to “No Screening”	-	27.7	28.0	28.6	29.3
compared to “No YouScreen”	-	-	35.1	48.2	57.2
Number of colposcopies needed to prevent one cervical cancer death					
compared to “No Screening”	-	76.1	76.9	77.8	80.3
compared to “No YouScreen”	-	-	92.2	106.5	147.0
Biopsies	0	19,049	20,068	20,445	21,212
Precancer treatments	0	7,420	7,749	7,869	8,032
Number needed to treat to prevent one cervical cancer case					
compared to “No Screening”	-	8.12	8.11	8.23	8.30
compared to “No YouScreen”	-	-	7.84	10.69	11.33
Number needed to treat to prevent one cervical cancer death					

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
compared to "No Screening"	-	22.35	22.27	22.42	22.75
compared to "No YouScreen"	-	-	21	24	29
Discounted measurements:					
Total costs	£4,034,415	£27,096,955	£27,632,154	£27,434,938	£28,144,943
Quality-adjusted life-years (QALYs)	4,163,789	4,165,869	4,165,942	4,165,960	4,165,992
Relative to "No Screening":					
Difference in total costs	-	£23,062,539	£23,597,739	£23,400,523	£24,110,527
QALYs gained	-	2,080	2,153	2,171	2,203
CER	-	£11,088	£10,960	£10,779	£10,944
Relative to "No YouScreen":					
Difference in total costs	-	-	£535,200	£337,983	£1,047,988
QALYs gained	-	-	73	91	123
CER	-	-	£7,332	£3,714	£8,520
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	£2,317	£1,053	£2,409
Incremental cost per extra CIN3+ detected	-	-	£3,850	£1,751	£4,658
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	Strongly dominated	£3,714	£22,188

Table 17 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when the costs and QALYs are undiscounted.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,783	5,856	5,859	5,937
Additional CIN2+ detected	-	-	73	76	154
CIN3+ detected	-	3,711	3,744	3,751	3,788

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Additional CIN3+ detected	-	-	33	40	77
Cervical cancer cases	1316	380	370	369	363
Cervical cancer incidence (ASR)	16.6	4.4	4.3	4.3	4.2
Cervical cancer cases prevented compared to:					
“No Screening”	-	936	946	947	953
“No YouScreen”	-	-	10	11	17
Cervical cancer deaths	457	119	115	115	115
Cervical cancer mortality (ASR)	5.50	1.31	1.28	1.28	1.26
Cervical cancer deaths prevented compared to:					
“No Screening”	-	338	342	342	342
“No YouScreen”	-	-	4	4	4
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.38%	0.37%	0.37%	0.36%
Death	0.46%	0.12%	0.12%	0.12%	0.12%
HPV tests	-	830,446	844,878	846,153	859,251
Average lifetime HPV tests per woman	-	8.30	8.45	8.46	8.59
Colposcopy evaluations	-	32,322	32,796	32,882	33,396
Number of colposcopies needed to prevent one cervical cancer case					
compared to “No Screening”	-	34.5	34.7	34.7	35.0
compared to “No YouScreen”	-	-	46.2	50.9	63.2
Number of colposcopies needed to prevent one cervical cancer death					
compared to “No Screening”	-	95.6	96.0	96.1	97.6
compared to “No YouScreen”	-	-	132.7	140.0	268.5
Biopsies	0	24,231	24,556	24,626	24,987
Precancer treatments	0	8,802	8,901	8,914	9,023
Number needed to treat to prevent one cervical cancer case					

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
compared to "No Screening"	-	9.40	9.41	9.41	9.47
compared to "No YouScreen"	-	-	9.67	10.18	13.00
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	26.04	26.06	26.06	26.38
compared to "No YouScreen"	-	-	28	28	55
Discounted measurements:					
Total costs	£9,950,545	£50,218,232	£50,301,251	£50,025,392	£50,131,923
Quality-adjusted life-years (QALYs)	7,121,988	7,130,228	7,130,310	7,130,307	7,130,348
Relative to "No Screening":					
Difference in total costs	-	£40,267,687	£40,350,706	£40,074,847	£40,181,378
QALYs gained	-	8,240	8,322	8,319	8,360
CER	-	£4,887	£4,849	£4,817	£4,806
Relative to "No YouScreen"					
Difference in total costs	-	-	83,019	-192840.00	-86309.00
QALYs gained	-	-	£82	£79	£120
CER	-	-	£1,016	-£2,441	-£719
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	£1,137	-£2,537	-£560
Incremental cost per extra CIN3+ detected	-	-	£2,490	-£4,821	-£1,121
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	1,016	Cost saving	Cost saving

Table 18 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when the lower bound of test positivity matrix (TPM) is assumed.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,783	5,819	5,833	5,865
Additional CIN2+ detected	-	-	36	50	82
CIN3+ detected	-	3,711	3,733	3,748	3,758
Additional CIN3+ detected	-	-	22	37	47
Cervical cancer cases	1316	380	371	371	368
Cervical cancer incidence (ASR)	16.6	4.4	4.3	4.3	4.2
Cervical cancer cases prevented compared to:					
“No Screening”	-	936	945	945	948
“No YouScreen”	-	-	9	9	12
Cervical cancer deaths	457	119	117	116	115
Cervical cancer mortality (ASR)	5.50	1.31	1.28	1.28	1.27
Cervical cancer deaths prevented compared to:					
“No Screening”	-	338	340	341	342
“No YouScreen”	-	-	2	3	4
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.38%	0.37%	0.37%	0.37%
Death	0.46%	0.12%	0.12%	0.12%	0.12%
HPV tests	-	830,446	844,697	845,765	858,633
Average lifetime HPV tests per woman	-	8.30	8.45	8.46	8.59
Colposcopy evaluations	-	32,322	32,363	32,480	32,510
Number of colposcopies needed to prevent one cervical cancer case					
compared to “No Screening”	-	34.5	34.2	34.4	34.3
compared to “No YouScreen”	-	-	4.6	17.6	15.7
Number of colposcopies needed to prevent one cervical cancer death					

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
compared to "No Screening"	-	95.6	95.2	95.2	95.1
compared to "No YouScreen"	-	-	20.5	52.7	47.0
Biopsies	0	24,231	24,262	24,353	24,365
Precancer treatments	0	8,802	8,828	8,860	8,899
Number needed to treat to prevent one cervical cancer case					
compared to "No Screening"	-	9.40	9.34	9.38	9.39
compared to "No YouScreen"	-	-	2.89	6.44	8.08
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	26.04	25.96	25.98	26.02
compared to "No YouScreen"	-	-	13	19	24
Discounted measurements:					
Total costs	£4,034,224	£33,962,012	£34,017,234	£33,869,760	£33,899,491
Quality-adjusted life-years (QALYs)	4,163,781	4,165,933	4,165,940	4,165,952	4,165,977
Relative to "No Screening"					
Difference in total costs	-	£29,927,788	£29,983,010	£29,835,536	£29,865,267
QALYs gained	-	2,152	2,159	2,171	2,196
CER	-	£13,907	£13,887	£13,743	£13,600
Relative to "No YouScreen"					
Difference in total costs	-	-	£55,222	-£92,252	-£62,521
QALYs gained	-	-	7	19	44
CER	-	-	£7,889	-£4,855	-£1,421
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	£1,534	-£1,845	-£762
Incremental cost per extra CIN3+ detected	-	-	£2,510	-£2,493	-£1,330

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	£7,889	Cost saving	Cost saving

Table 19 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when no hysterectomy was ever performed.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,902	5,978	5,996	6,059
Additional CIN2+ detected	-	-	76	94	157
CIN3+ detected	-	3,804	3,838	3,848	3,882
Additional CIN3+ detected	-	-	34	44	78
Cervical cancer cases	1,600	479	475	470	462
Cervical cancer incidence (ASR)	19.70	5.49	5.41	5.36	5.28
Cervical cancer cases prevented compared to					
“No Screening”	-	1121	1125	1130	1138
“No YouScreen”	-	-	4	9	17
Cervical cancer deaths	575	156	153	151	151
Cervical cancer mortality (ASR)	6.80	1.72	1.65	1.63	1.63
Cervical cancer deaths prevented compared to:					
“No Screening”	-	419	422	424	424
“No YouScreen”	-	-	3	5	5
Cumulative life risk of cervical cancer: diagnosis	1.60%	0.48%	0.48%	0.47%	0.46%
Death	0.58%	0.16%	0.15%	0.15%	0.15%
HPV tests	-	924,270	939,185	940,661	954,054
Average lifetime HPV tests per woman	-	9.24	9.39	9.41	9.54

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Colposcopy evaluations	-	33,151	33,678	33,753	34,274
Number of colposcopies needed to prevent one cervical cancer case					
compared to "No Screening"	-	29.6	29.9	29.9	30.1
compared to "No YouScreen"	-	-	131.7	66.9	66.1
Number of colposcopies needed to prevent one cervical cancer death					
compared to "No Screening"	-	79.1	79.8	79.6	80.8
compared to "No YouScreen"	-	-	175.6	120.4	224.6
Biopsies	0	24,727	25,101	25,168	25,465
Precancer treatments	0	9,034	9,127	9,154	9,230
Number needed to treat to prevent one cervical cancer case					
compared to "No Screening"	-	8.06	8.11	8.10	8.11
compared to "No YouScreen"	-	-	23.25	13.33	11.53
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	21.56	21.63	21.59	21.77
compared to "No YouScreen"	-	-	31	24	39
Discounted measurements:					
Total costs	£4,721,650	£35,724,432	£35,951,906	£35,781,206	£35,977,498
Quality-adjusted life-years (QALYs)	4,163,432	4,165,873	4,165,898	4,165,899	4,165,900
Relative to "No Screening"					
Difference in total costs	-	£31,002,782	£31,230,256	£31,059,556	£31,255,848
QALYs gained	-	2,441	2,466	2,467	2,468
CER	-	£12,701	£12,664	£12,590	£12,664
Relative to "No YouScreen"					
Difference in total costs	-	-	£227,474	£56,774	£253,066
QALYs gained	-	-	25	26	27
CER	-	-	£9,099	£2,184	£9,373
Incremental cost per additional:					

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Incremental cost per extra CIN2+ detected	-	-	£2,988	£604	£1,612
Incremental cost per extra CIN3+ detected	-	-	£6,690	£1,290	£3,244
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	<i>Strongly dominated</i>	£2,184	£196,292

Table 20 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when the YouScreen self-sampling kits are offered from one-year late.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,783	5,846	5,841	5,896
Additional CIN2+ detected	-	-	63	58	113
CIN3+ detected	-	3,711	3,750	3,744	3,767
Additional CIN3+ detected	-	-	39	33	56
Cervical cancer cases	1316	380	369	368	363
Cervical cancer incidence (ASR)	16.6	4.4	4.3	4.3	4.2
Cervical cancer cases prevented compared to					
“No Screening”	-	936	947	948	953
“No YouScreen”	-	-	11	12	17
Cervical cancer deaths	457	119	116	116	113
Cervical cancer mortality (ASR)	5.50	1.31	1.30	1.28	1.25
Cervical cancer deaths prevented compared to:					
“No Screening”	-	338	341	341	344
“No YouScreen”	-	-	3	3	6
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.38%	0.37%	0.37%	0.36%

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Death	0.46%	0.12%	0.12%	0.12%	0.11%
HPV tests	-	830,446	834,997	836,088	839,659
Average lifetime HPV tests per woman	-	8.30	8.35	8.36	8.40
Colposcopy evaluations	-	32,322	32,698	32,690	33,100
Number of colposcopies needed to prevent one cervical cancer case					
compared to "No Screening"	-	34.5	34.5	34.5	34.7
compared to "No YouScreen"	-	-	34.2	30.7	45.8
Number of colposcopies needed to prevent one cervical cancer death					
compared to "No Screening"	-	95.6	95.9	95.9	96.2
compared to "No YouScreen"	-	-	125.3	122.7	129.7
Biopsies	0	24,231	24,490	24,479	24,763
Precancer treatments	0	8,802	8,886	8,873	8,959
Number needed to treat to prevent one cervical cancer case					
compared to "No Screening"	-	9.40	9.38	9.36	9.40
compared to "No YouScreen"	-	-	7.64	5.92	9.24
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	26.04	26.06	26.02	26.04
compared to "No YouScreen"	-	-	28	24	26
Discounted measurements:					
Total costs	£4,034,224	£33,962,012	£33,952,528	£33,799,030	£33,806,172
Quality-adjusted life-years (QALYs)	4,163,781	4,165,933	4,165,935	4,165,957	4,165,978
Relative to "No Screening"					
Difference in total costs	-	£29,927,788	£29,918,304	£29,764,806	£29,771,948
QALYs gained	-	2,152	2,154	2,176	2,197
CER	-	£13,907	£13,890	£13,679	£13,551
Relative to "No YouScreen"					

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Difference in total costs	-	-	-£9,484	-£162,982	-£155,840
QALYs gained	-	-	2	24	45
CER	-	-	-£4,742	-£6,791	-£3,463
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	-£151	-£2,810	-£1,379
Incremental cost per extra CIN3+ detected	-	-	-£243	-£4,939	-£2,783
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	Cost saving	Cost saving	Cost saving

Table 21 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when upper bound of HPV test costs are assumed.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,783	5,856	5,859	5,937
Additional CIN2+ detected	-	-	73	76	154
CIN3+ detected	-	3,711	3,744	3,751	3,788
Additional CIN3+ detected	-	-	33	40	77
Cervical cancer cases	1316	380	370	369	363
Cervical cancer incidence (ASR)	16.6	4.4	4.3	4.3	4.2
Cervical cancer cases prevented compared to					
“No Screening”	-	936	946	947	953
“No YouScreen”	-	-	10	11	17
Cervical cancer deaths	457	119	115	115	115
Cervical cancer mortality (ASR)	5.50	1.31	1.28	1.28	1.26
Cervical cancer deaths prevented compared to:					

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
"No Screening"	-	338	342	342	342
"No YouScreen"	-	-	4	4	4
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.38%	0.37%	0.37%	0.36%
Death	0.46%	0.12%	0.12%	0.12%	0.12%
HPV tests	-	830,446	844,878	846,153	859,251
Average lifetime HPV tests per woman	-	8.30	8.45	8.46	8.59
Colposcopy evaluations	-	32,322	32,796	32,882	33,396
Number of colposcopies needed to prevent one cervical cancer case					
compared to "No Screening"	-	34.5	34.7	34.7	35.0
compared to "No YouScreen"	-	-	46.2	50.9	63.2
Number of colposcopies needed to prevent one cervical cancer death					
compared to "No Screening"	-	95.6	96.0	96.1	97.6
compared to "No YouScreen"	-	-	132.7	140.0	268.5
Biopsies	0	24,231	24,556	24,626	24,987
Precancer treatments	0	8,802	8,901	8,914	9,023
Number needed to treat to prevent one cervical cancer case					
compared to "No Screening"	-	9.40	9.41	9.41	9.47
compared to "No YouScreen"	-	-	9.67	10.18	13.00
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	26.04	26.06	26.06	26.38
compared to "No YouScreen"	-	-	28	28	55
Discounted measurements:					
Total costs	£4,034,224	£33,962,012	£34,638,900	£34,473,160	£35,121,578
Quality-adjusted life-years (QALYs)	4,163,781	4,165,933	4,165,957	4,165,958	4,165,967
Relative to "No Screening"					

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Difference in total costs	-	£29,927,788	£30,604,676	£30,438,936	£31,087,354
QALYs gained	-	2,152	2,176	2,177	2,186
CER	-	£13,907	£14,066	£13,982	£14,221
Relative to "No YouScreen"					
Difference in total costs	-	-	£676,888	£511,148	£1,159,566
QALYs gained	-	-	24	25	34
CER	-	-	£28,395	£20,446	£34,105
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	£9,267	£6,726	£7,530
Incremental cost per extra CIN3+ detected	-	-	£20,302	£12,779	£15,059
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	Strongly dominated	£20,446	£72,046

Table 22 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when upper bound of all costs are assumed (see Table 3 for details).

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,783	5,856	5,859	5,937
Additional CIN2+ detected	-	-	73	76	154
CIN3+ detected	-	3,711	3,744	3,751	3,788
Additional CIN3+ detected	-	-	33	40	77
Cervical cancer cases	1316	380	370	369	363
Cervical cancer incidence (ASR)	16.6	4.4	4.3	4.3	4.2
Cervical cancer cases prevented compared to					
"No Screening"	-	936	946	947	953
"No YouScreen"	-	-	10	11	17

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Cervical cancer deaths	457	119	115	115	115
Cervical cancer mortality (ASR)	5.50	1.31	1.28	1.28	1.26
Cervical cancer deaths prevented compared to:					
“No Screening”	-	338	342	342	342
“No YouScreen”	-	-	4	4	4
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.38%	0.37%	0.37%	0.36%
Death	0.46%	0.12%	0.12%	0.12%	0.12%
HPV tests	-	830,446	844,878	846,153	859,251
Average lifetime HPV tests per woman	-	8.30	8.45	8.46	8.59
Colposcopy evaluations	-	32,322	32,796	32,882	33,396
Number of colposcopies needed to prevent one cervical cancer case					
compared to “No Screening”	-	34.5	34.7	34.7	35.0
compared to “No YouScreen”	-	-	46.2	50.9	63.2
Number of colposcopies needed to prevent one cervical cancer death					
compared to “No Screening”	-	95.6	96.0	96.1	97.6
compared to “No YouScreen”	-	-	132.7	140.0	268.5
Biopsies	0	24,231	24,556	24,626	24,987
Precancer treatments	0	8,802	8,901	8,914	9,023
Number needed to treat to prevent one cervical cancer case					
compared to “No Screening”	-	9.40	9.41	9.41	9.47
compared to “No YouScreen”	-	-	9.67	10.18	13.00
Number needed to treat to prevent one cervical cancer death					
compared to “No Screening”	-	26.04	26.06	26.06	26.38
compared to “No YouScreen”	-	-	28	28	55

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
<i>Discounted measurements:</i>					
Total costs	£4,034,224	£36,513,438	£37,231,193	£37,069,685	£37,761,140
Quality-adjusted life-years (QALYs)	4,163,781	4,165,933	4,165,957	4,165,958	4,165,967
Relative to "No Screening"					
Difference in total costs	-	£32,479,214	£33,196,969	£33,035,461	£33,726,916
QALYs gained	-	2,152	2,176	2,177	2,186
CER	-	£15,093	£15,257	£15,175	£15,429
Relative to "No YouScreen"					
Difference in total costs	-	-	£717,755	£556,247	£1,24,702
QALYs gained	-	-	24	25	34
CER	-	-	£30,110	£22,250	£36,697
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	£9,827	£7,319	£8,102
Incremental cost per extra CIN3+ detected	-	-	£21,527	£13,906	£16,204
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	Strongly dominated	£22,250	£76,828

Table 23 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when lower bound of HPV and LBC tests costs are implemented.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,783	5,856	5,859	5,937
Additional CIN2+ detected	-	-	73	76	154
CIN3+ detected	-	3,711	3,744	3,751	3,788
Additional CIN3+ detected	-	-	33	40	77
Cervical cancer cases	1316	380	370	369	363

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Cervical cancer incidence (ASR)	16.6	4.4	4.3	4.3	4.2
Cervical cancer cases prevented compared to					
“No Screening”	-	936	946	947	953
“No YouScreen”	-	-	10	11	17
Cervical cancer deaths	457	119	115	115	115
Cervical cancer mortality (ASR)	5.50	1.31	1.28	1.28	1.26
Cervical cancer deaths prevented compared to:					
“No Screening”	-	338	342	342	342
“No YouScreen”	-	-	4	4	4
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.38%	0.37%	0.37%	0.36%
Death	0.46%	0.12%	0.12%	0.12%	0.12%
HPV tests	-	830,446	844,878	846,153	859,251
Average lifetime HPV tests per woman	-	8.30	8.45	8.46	8.59
Colposcopy evaluations	-	32,322	32,796	32,882	33,396
Number of colposcopies needed to prevent one cervical cancer case					
compared to “No Screening”	-	34.5	34.7	34.7	35.0
compared to “No YouScreen”	-	-	46.2	50.9	63.2
Number of colposcopies needed to prevent one cervical cancer death					
compared to “No Screening”	-	95.6	96.0	96.1	97.6
compared to “No YouScreen”	-	-	132.7	140.0	268.5
Biopsies	0	24,231	24,556	24,626	24,987
Precancer treatments	0	8,802	8,901	8,914	9,023
Number needed to treat to prevent one cervical cancer case					
compared to “No Screening”	-	9.40	9.41	9.41	9.47
compared to “No YouScreen”	-	-	9.67	10.18	13.00

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	26.04	26.06	26.06	26.38
compared to "No YouScreen"	-	-	28	28	55
Discounted measurements:					
Total costs	£4,034,224	£31,925,809	£32,108,221	£31,939,303	£32,121,670
Quality-adjusted life-years (QALYs)	4,163,781	4,165,933	4,165,957	4,165,958	4,165,967
Relative to "No Screening"					
Difference in total costs	-	£27,891,585	£28,073,997	£27,905,079	£28,087,446
QALYs gained	-	2,152	2,176	2,177	2,186
CER	-	£12,961	£12,903	£12,818	£12,849
Relative to "No YouScreen"					
Difference in total costs	-	-	£182,412	£13,494	£195,861
QALYs gained	-	-	24	25	34
CER	-	-	£7,652	£540	£5,761
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	£2,497	£178	£1,272
Incremental cost per extra CIN3+ detected	-	-	£5,471	£337	£2,544
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	Strongly dominated	£540	£20,263

Table 24 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when lower bound of all costs are implemented (see Table 3 for details).

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,783	5,856	5,859	5,937
Additional CIN2+ detected	-	-	73	76	154

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN3+ detected	-	3,711	3,744	3,751	3,788
Additional CIN3+ detected	-	-	33	40	77
Cervical cancer cases	1316	380	370	369	363
Cervical cancer incidence (ASR)	16.6	4.4	4.3	4.3	4.2
Cervical cancer cases prevented compared to					
“No Screening”	-	936	946	947	953
“No YouScreen”	-	-	10	11	17
Cervical cancer deaths	457	119	115	115	115
Cervical cancer mortality (ASR)	5.50	1.31	1.28	1.28	1.26
Cervical cancer deaths prevented compared to:					
“No Screening”	-	338	342	342	342
“No YouScreen”	-	-	4	4	4
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.38%	0.37%	0.37%	0.36%
Death	0.46%	0.12%	0.12%	0.12%	0.12%
HPV tests	-	830,446	844,878	846,153	859,251
Average lifetime HPV tests per woman	-	8.30	8.45	8.46	8.59
Colposcopy evaluations	-	32,322	32,796	32,882	33,396
Number of colposcopies needed to prevent one cervical cancer case					
compared to “No Screening”	-	34.5	34.7	34.7	35.0
compared to “No YouScreen”	-	-	46.2	50.9	63.2
Number of colposcopies needed to prevent one cervical cancer death					
compared to “No Screening”	-	95.6	96.0	96.1	97.6
compared to “No YouScreen”	-	-	132.7	140.0	268.5
Biopsies	0	24,231	24,556	24,626	24,987
Precancer treatments	0	8,802	8,901	8,914	9,023

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Number needed to treat to prevent one cervical cancer case					
compared to "No Screening"	-	9.40	9.41	9.41	9.47
compared to "No YouScreen"	-	-	9.67	10.18	13.00
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	26.04	26.06	26.06	26.38
compared to "No YouScreen"	-	-	28	28	55
Discounted measurements:					
Total costs	£4,034,224	£30,105,024	£30,256,939	£30,084,487	£30,234,558
Quality-adjusted life-years (QALYs)	4,163,781	4,165,933	4,165,957	4,165,958	4,165,967
Relative to "No Screening"					
Difference in total costs	-	£26,070,800	£26,222,715	£26,050,263	£26,200,334
QALYs gained	-	2,152	2,176	2,177	2,186
CER	-	£12,115	£12,052	£11,966	£11,986
Relative to "No YouScreen"					
Difference in total costs	-	-	£151,916	-£20,537	£129,534
QALYs gained	-	-	24	25	34
CER	-	-	£6,373	cost saving	£3,810
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	£2,0807	cost saving	£841
Incremental cost per extra CIN3+ detected	-	-	£4,556	cost saving	£1,682
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	Strongly dominated	Cost saving	£3,810

Table 25 Summary of model findings for a cohort of 100,000 women turning 26 in 2021 when alternative disutility weights are implemented.

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
CIN2+ detected	-	5,783	5,856	5,859	5,937
Additional CIN2+ detected	-	-	73	76	154
CIN3+ detected	-	3,711	3,744	3,751	3,788
Additional CIN3+ detected	-	-	33	40	77
Cervical cancer cases	1316	380	370	369	363
Cervical cancer incidence (ASR)	16.6	4.4	4.3	4.3	4.2
Cervical cancer cases prevented compared to					
“No Screening”	-	936	946	947	953
“No YouScreen”	-	-	10	11	17
Cervical cancer deaths	457	119	115	115	115
Cervical cancer mortality (ASR)	5.50	1.31	1.28	1.28	1.26
Cervical cancer deaths prevented compared to:					
“No Screening”	-	338	342	342	342
“No YouScreen”	-	-	4	4	4
Cumulative life risk of cervical cancer: diagnosis	1.32%	0.38%	0.37%	0.37%	0.36%
Death	0.46%	0.12%	0.12%	0.12%	0.12%
HPV tests	-	830,446	844,878	846,153	859,251
Average lifetime HPV tests per woman	-	8.30	8.45	8.46	8.59
Colposcopy evaluations	-	32,322	32,796	32,882	33,396
Number of colposcopies needed to prevent one cervical cancer case					
compared to “No Screening”	-	34.5	34.7	34.7	35.0
compared to “No YouScreen”	-	-	46.2	50.9	63.2
Number of colposcopies needed to prevent one cervical cancer death					
compared to “No Screening”	-	95.6	96.0	96.1	97.6
compared to “No YouScreen”	-	-	132.7	140.0	268.5
Biopsies	0	24,231	24,556	24,626	24,987

Outcome	No Screening	No YouScreen (status quo)	Mail-out only	YouScreen (GP opportunistic only)	YouScreen (GP opportunistic and direct Mail-out)
Precancer treatments	0	8,802	8,901	8,914	9,023
Number needed to treat to prevent one cervical cancer case					
compared to "No Screening"	-	9.40	9.41	9.41	9.47
compared to "No YouScreen"	-	-	9.67	10.18	13.00
Number needed to treat to prevent one cervical cancer death					
compared to "No Screening"	-	26.04	26.06	26.06	26.38
compared to "No YouScreen"	-	-	28	28	55
Discounted measurements:					
Total costs	£4,034,224	£33,962,012	£34,185,904	£34,019,124	£34,240,178
Quality-adjusted life-years (QALYs)	4,163,825	4,166,075	4,166,100	4,166,101	4,166,112
Relative to "No Screening"					
Difference in total costs	-	£29,927,788	£30,151,680	£29,984,900	£30,205,954
QALYs gained	-	2,250	2,275	2,276	2,287
CER	-	£13,301	£13,253	£13,174	£13,208
Relative to "No YouScreen"					
Difference in total costs	-	-	£223,892	£57,112	£278,166
QALYs gained	-	-	25	26	37
CER	-	-	£8,956	£2,197	£7,518
Incremental cost per additional:					
Incremental cost per extra CIN2+ detected	-	-	£3,065	£751	£1,806
Incremental cost per extra CIN3+ detected	-	-	£6,715	£1,428	£3,613
Incremental cost-effectiveness ratio (ICER) per QALY saved	-	-	Strongly dominated*	£2,197	£20,096

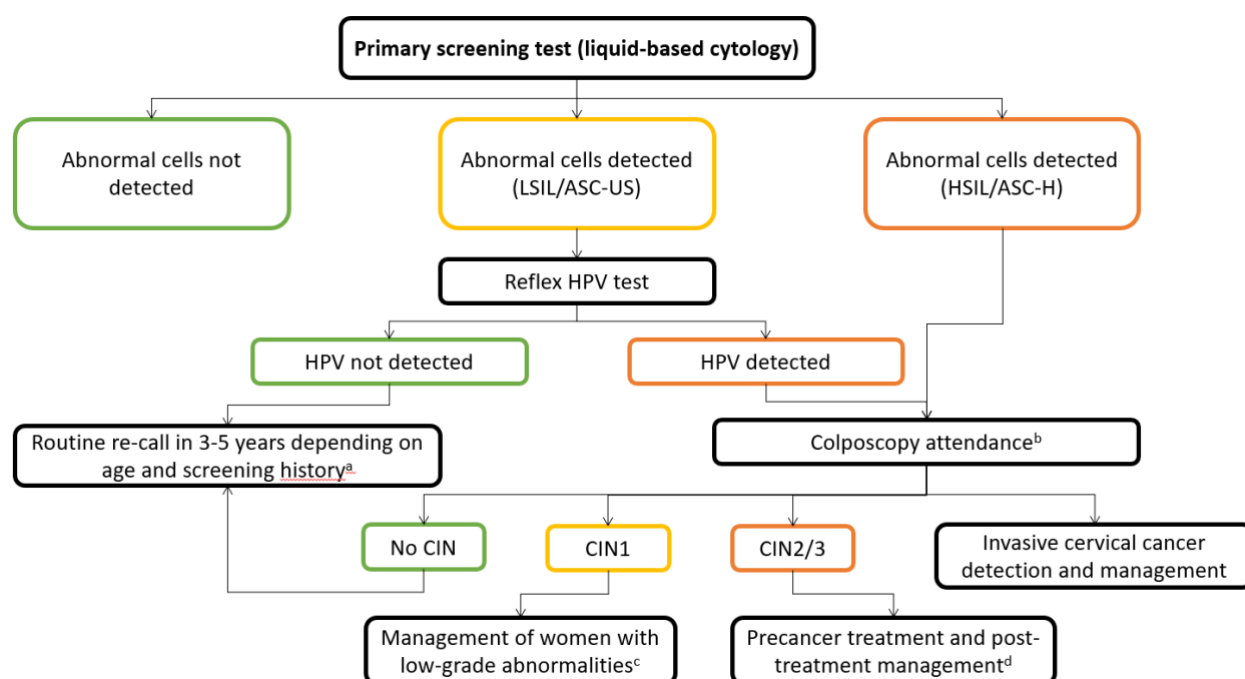
* Any strategy with lower effectiveness but higher costs than another strategy is said to be "strongly dominated".

Appendix 1: Model calibration to England

The following material outlines additional background methodological details relevant to the structure, features, calibration, and validation of the Policy-Cervix model platform. This appendix has been reproduced with minor adaptations the published material.

Cervical screening programme management

Primary Cytology Testing (HPV Triage)



Primary HPV Testing

Cervical screening programme management primary HPV testing with cytology triage are based on 2021 guidelines released by the NHS.³⁹ This management is outlined in Figure 15, Figure 16 and Figure 17.

Figure 15 Management of women at their primary HPV test (including follow-up in 12 months for hrHPV positive women with normal cytology).

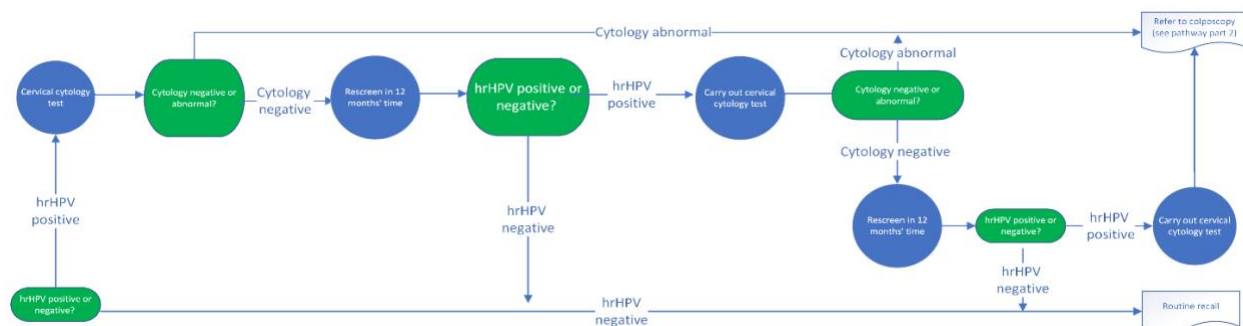


Figure 16 Management of women at colposcopy evaluation.

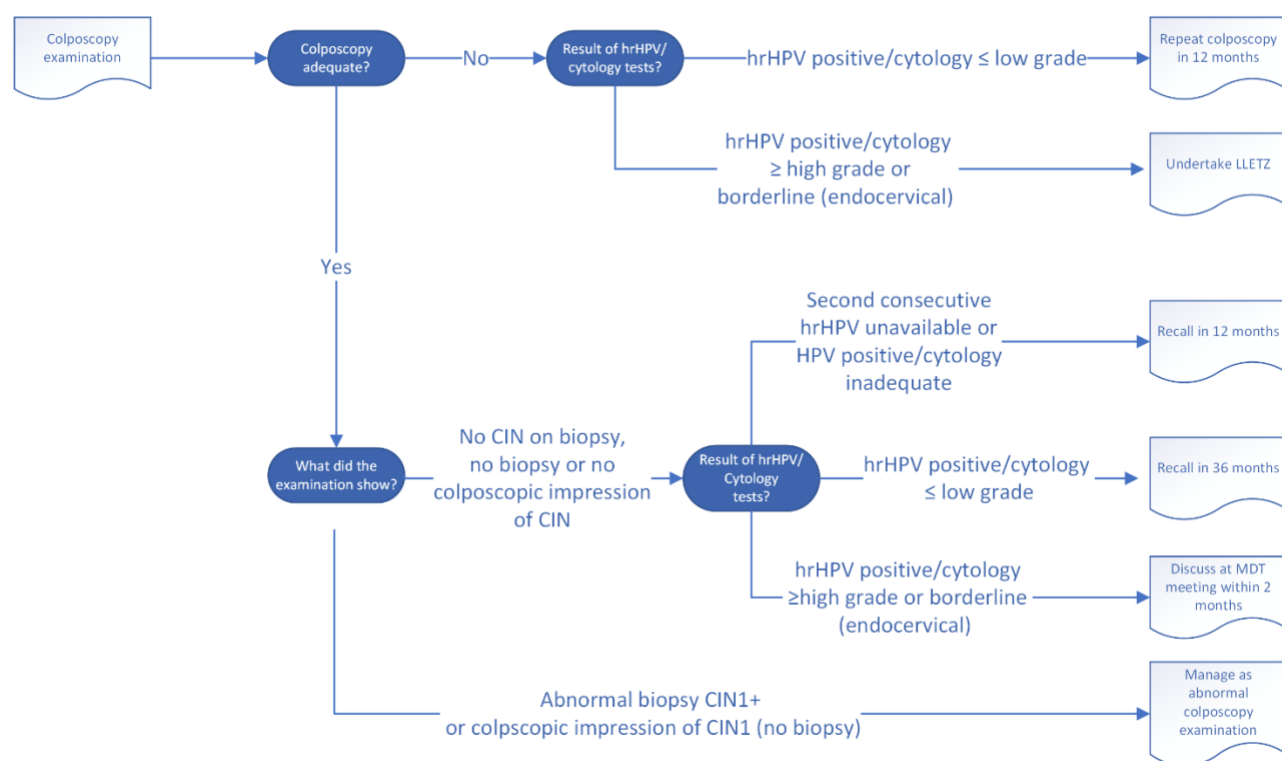
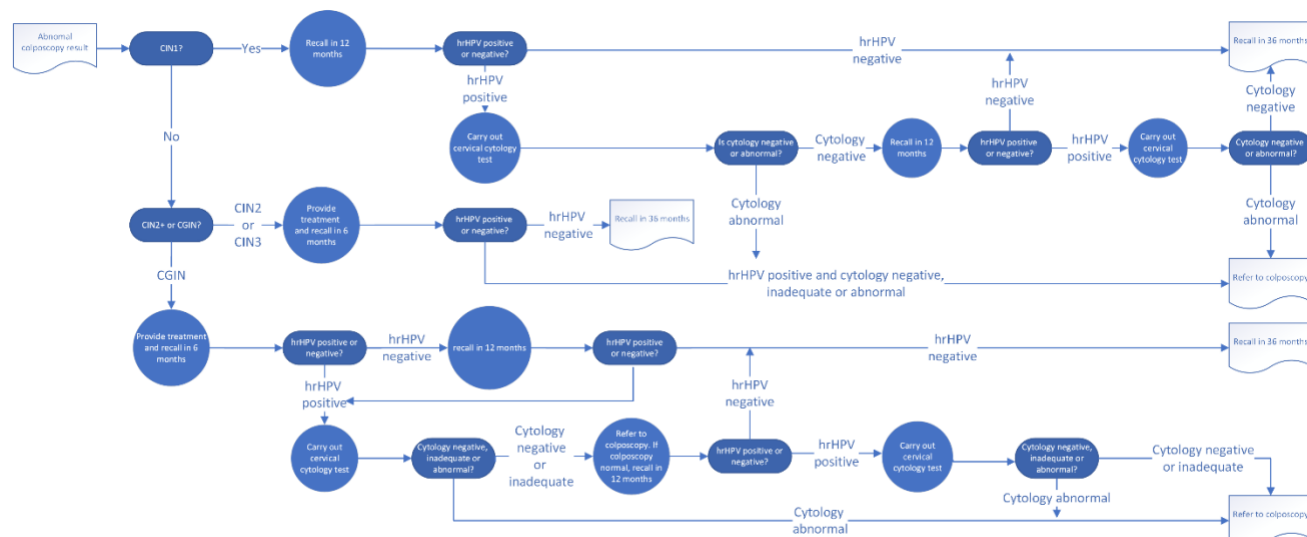


Figure 17 Management of women following colposcopy evaluation with abnormal findings.



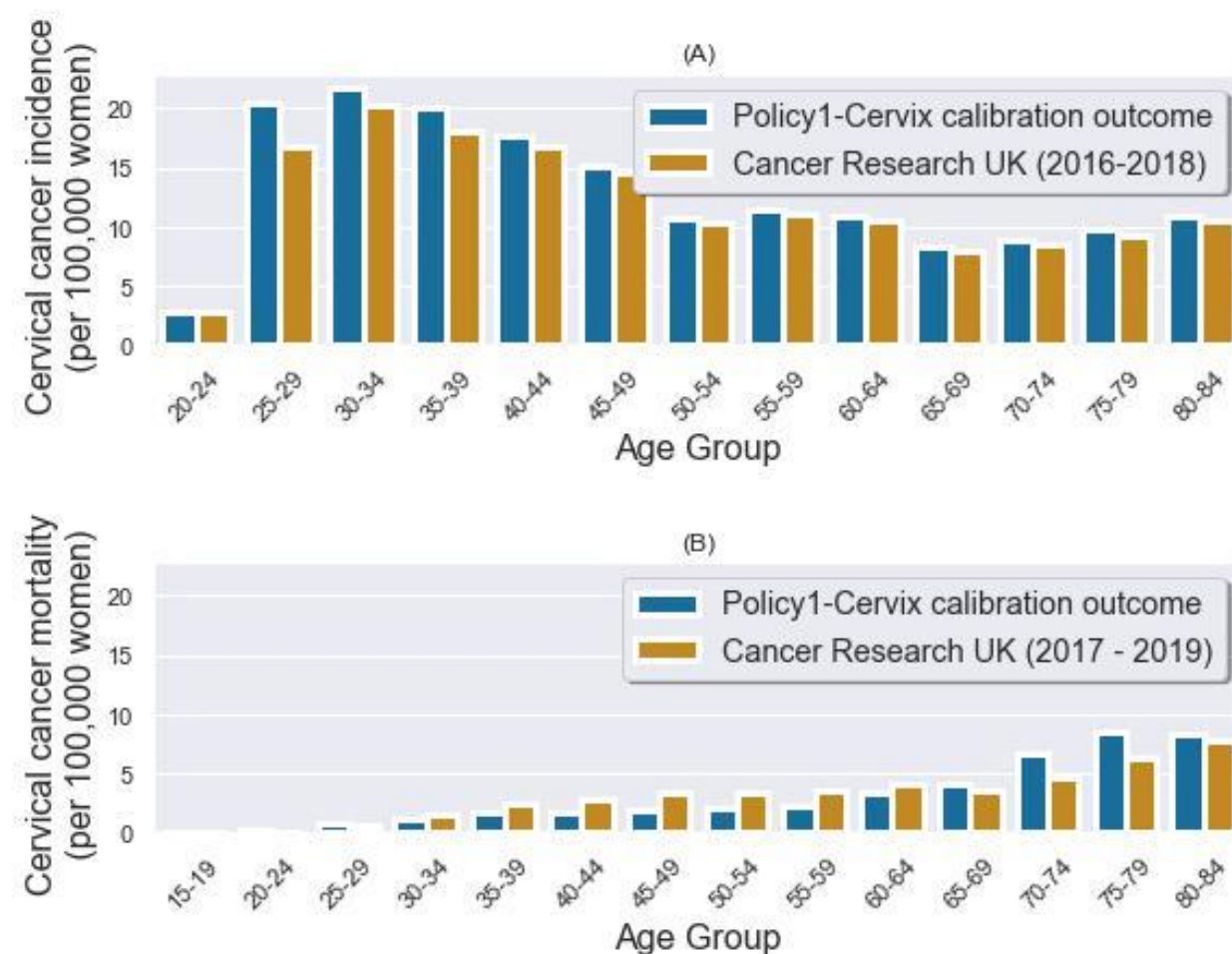
Calibration to England

In order to simulate the YouScreen trial in England, the *Policy1-Cervix* platform must reproduce age-specific risks of HPV-related cervical disease for the simulated years. To assess the validity of our assumptions for cervical disease, we compare model generated outputs with real-life data specific to the setting. In order to do this, we configured the model to replicate the previous and current cervical screening programmes (primary cytology and primary HPV) in England, and, the national HPV vaccination programme, as described in sections titled *Cervical screening programme management* and *HPV immunisation programme features and coverage* respectively. The calibration process does not consider the YouScreen trial, as the purpose of the calibration is to determine underlying cervical cancer risk among women in England more generally.

Here, we compare outputs from *Policy1-Cervix* to age-specific cervical cancer incidence and mortality rates (Figure 18), age-specific detection rates of low-grade and high-grade cervical disease under the previous cytology-based screening programme (Figure 20), and age-specific HPV prevalence (Figure 21).

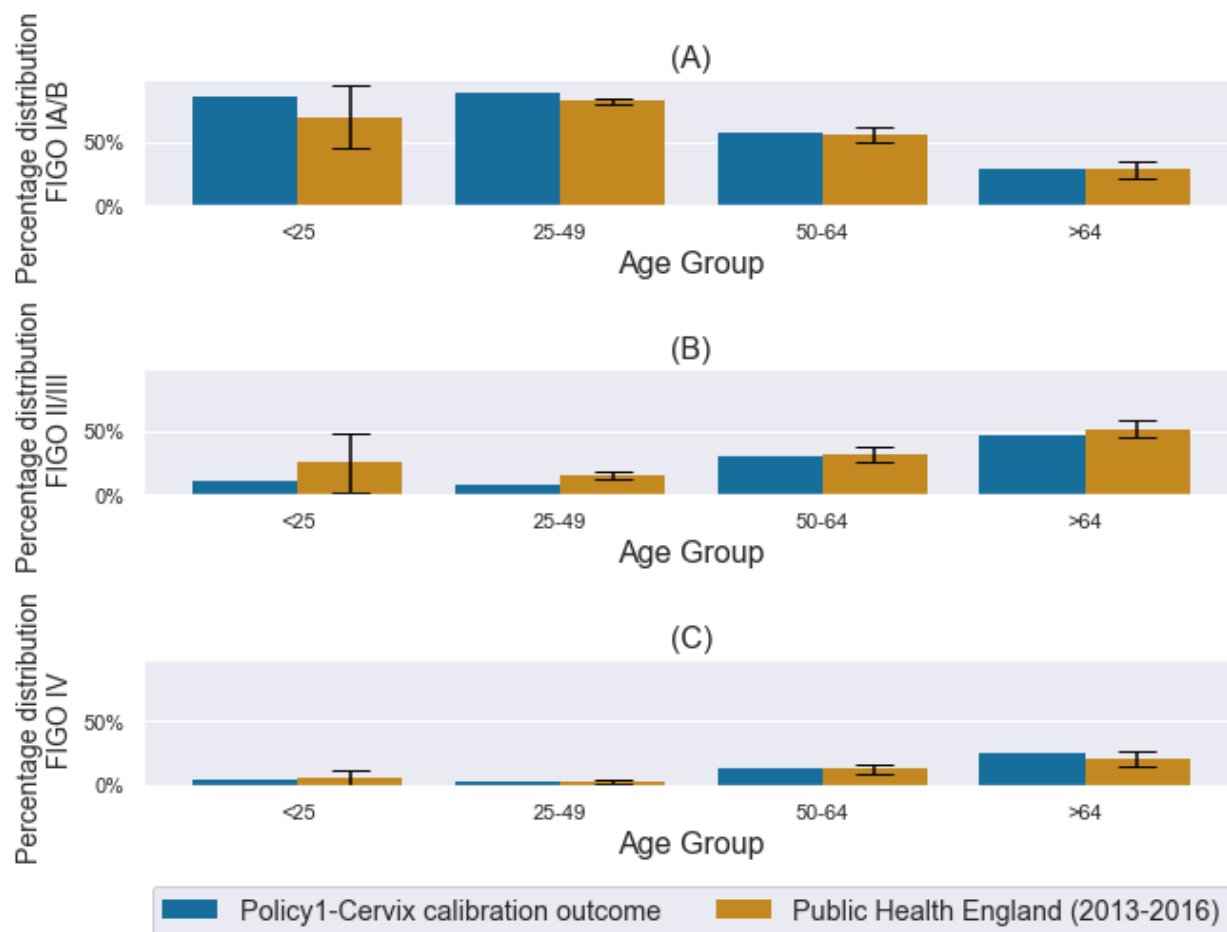
Fitting the *Policy1-Cervix* model output to cervical cancer incidence in England was challenging, due largely to the high observed rates of cervical cancer incidence among young English women compared to other high-income countries, and the calibration outcome reflects this (Figure 18A). One suggestion for why this is the case was variation in reporting of CIN3/pre-invasive lesions versus cervical cancer (ie misclassification of some carcinoma in situ as cervical cancer). To account for this when comparing to observed data, the modelling accounts for 1-3% of CIN3 being misclassified as cervical cancer in routine statistics. Notably, despite discordance between the data and model predictions for cervical cancer incidence, model predicted cervical cancer mortality rates are a reasonable match to the observed data (Figure 18B). The assumed misclassification was not carried through to the main analysis, as it could not be guaranteed this would continue.

Figure 18 *Policy1-Cervix* versus observed age-specific cervical cancer incidence (A) and mortality (B) rates per 100,000 women.



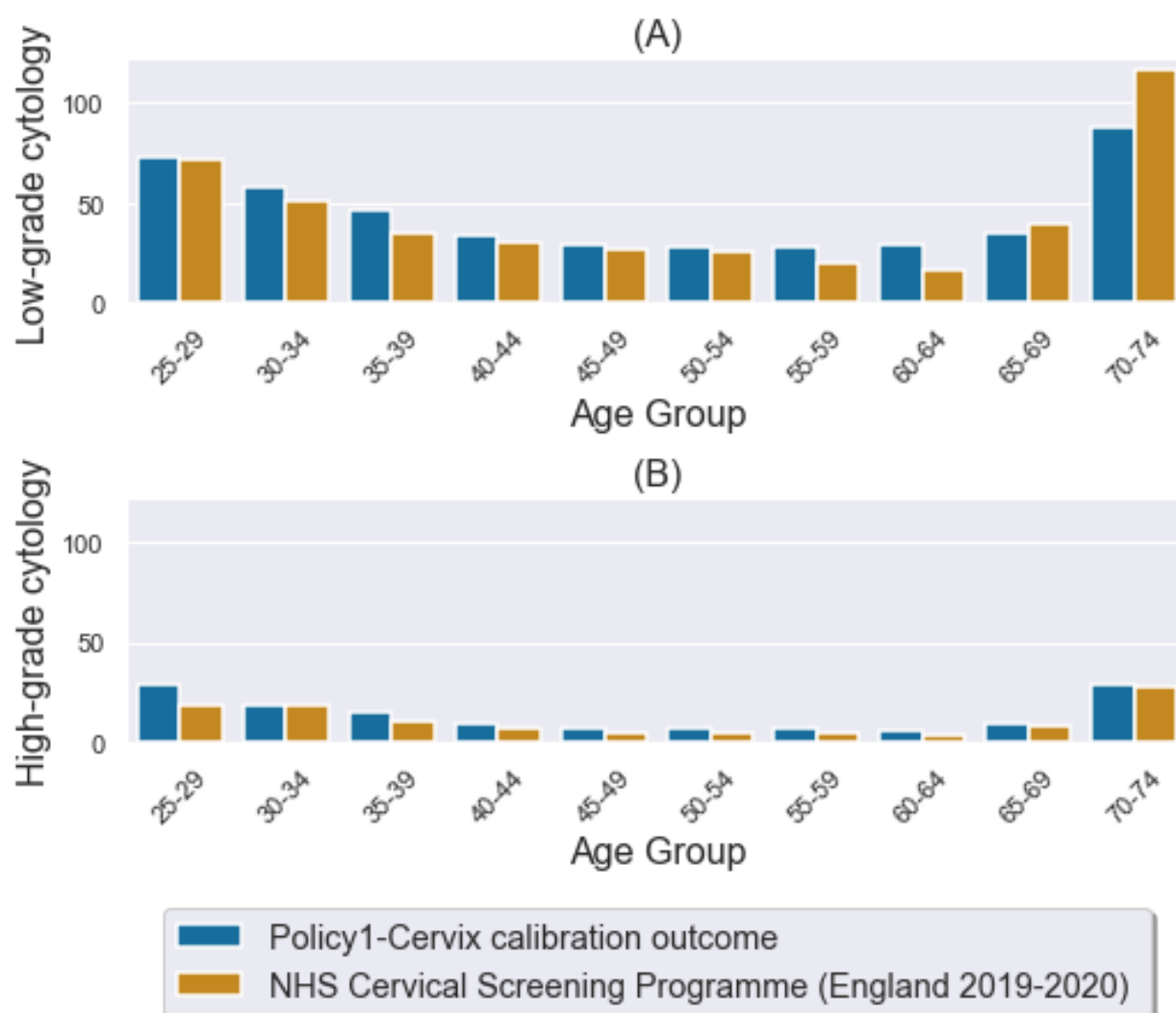
For women diagnosed with cervical cancer, the *Policy1-Cervix* estimated distribution (percent) of stage at diagnosis is comparable to observed distribution of cancer stages in England.⁴⁰ A comparison of *Policy1-Cervix* to the observed stage distribution is presented below.

Figure 19 *Policy1-Cervix* versus observed age-specific cervical cancer incidence rates at stages (A) FIGO IA/B (B) FIGO II/III and (C) FIGO IV, per 100,000 women.



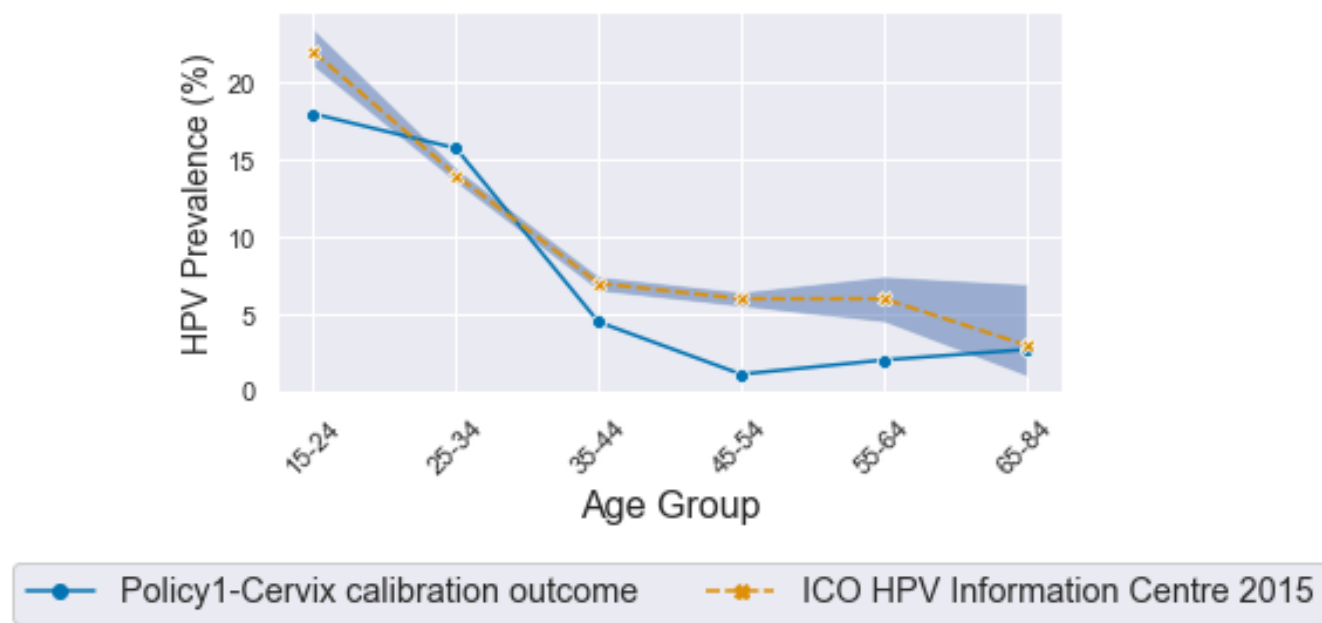
In a simulated scenario where cervical screening is delivered under the previous guidelines for primary cytology with HPV triage, *Policy1-Cervix* reports rates of cytologically-detected LSIL and HSIL which are consistent with observed NHS data (Figure 20).⁴⁰

Figure 20 *Policy1-Cervix* versus observed age-specific rates of (A) low-grade and (B) high-grade cytology per 1,000 women screened.



Policy1-Cervix estimates for age-specific HPV prevalence broadly match the trends evident in available data, which is sourced from systematic reviews and meta-analysis performed by ICO (Figure 21). Notably however, the model predicted HPV prevalence in women aged 30 years and over is lower than the observed data. We have decided to accept this in favour of creating a better model fit to the above rates of cytological findings as presented in Figure 20, as the cytology outcome data is both more recent and based on a larger data set of routine screening outcomes.

Figure 21 *Policy1-Cervix* versus observed age-specific HPV prevalence in England.



Appendix 2: Additional exploratory scenarios

To verify the impact of model parameter inputs relating to screening behaviour on predicted screening coverage, we ran additional exploratory simulations to ensure that results were consistent with what was expected.

We simulated 15 screening scenarios for a cohort⁸ of 10,000,000 unvaccinated women who entered the YouScreen trial when aged 26. In this cohort, the impact of YouScreen on their screening participation is via a boost on screening initiation, and not via re-attendance rate (since those aged 26 who have already attended would not be considered late). The status quo screening initiation is obtained via calibration to England screening coverage data in 2022⁵. In the status quo screening scenario (no YouScreen), the model predicts that the screening participation among women aged 25-64 years in terms of those who are up to date with screening (screened in the last 3.5 years for ages 25-49; screened in the last 5.5 years for ages 50-64) is 68.12%; model-predicted screening participation is estimated to be 72.76% for direct mail-out, 72.96% for YouScreen (GP opportunistic), and 74.35% for YouScreen (GP opportunistic and mail-out combined).

The exploratory simulations, including the expected and actual impact of various inputs on on-time screening coverage are shown in Table 26. The model-predicted screening coverage in the exploratory simulations align with the expected predictions. This verifies that the model is behaving as expected in response to changes in model inputs relating to screening behaviour.

Table 26 Table of exploratory scenarios to demonstrate the impact of inputs on screening participation outputs.

Initiation boost (amount)	What is expected	Screening coverage predicted by the model		Interpretation of the results
		Observed	Expected	
For YouScreen (GP opportunistic), the model assumes 7.7% self-sampling uptake rate in 2021, 2022, and 2023. By reducing self-sampling uptake rate via multiplying it with a percentage value, we aim to test the impact of incrementally increasing the "boost" on resulting screening participation. The percentages are:				
0%	This is equivalent to No YouScreen	68.3%	68.12%	The model works as expected. Due to the stochastic nature of the modelling, a small difference compared to expected value is reasonable.
10%	Screening coverage is predicted to increase	68.45%	68.60%	The model works as expected.

⁸ For all the scenarios, we simulated a cohort of 100,000 or 10,000,000 women for stability of model estimates and is not intended to directly relate to a real-life birth cohort.

Initiation boost (amount)	What is expected	Screening coverage predicted by the model		Interpretation of the results
		Observed	Expected	
	by 10% of size of the increase in the YouScreen (GP opportunistic) scenario			
20%	Screening coverage is predicted to increase by 20% of size of the increase in the YouScreen (GP opportunistic) scenario	69.10%	69.06%	The model works as expected.
60%	Screening coverage is predicted to increase by 60% of size of the increase in the YouScreen (GP opportunistic) scenario	70.90%	71.02%	The model works as expected.
100%	This is equivalent to YouScreen (GP opportunistic)	73.10%	72.96%	The model works as expected.
For direct Mail-out, 12.9% self-sampling uptake rate, offered in 2021. Similarly, the percentage values are:				
0%	This is equivalent to No YouScreen	68.20%	68.12%	The model works as expected.
10%	Screening coverage is predicted to increase by 10% of size of the increase in the Direct Mailout scenario	68.66%	68.58%	The model works as expected.
20%	Screening coverage is predicted to increase by 20% of size of the increase in the Direct Mailout scenario	68.90%	69.05%	The model works as expected.
60%	Screening coverage is predicted to increase by 60% of size of the increase in the Direct Mailout scenario	71.05%	70.90%	The model works as expected.
100%	This is equivalent to direct Mail-out	72.88%	72.76%	The model works as expected.
For YouScreen (combined approach), 20.6% self-sampling uptake rate, offered in 2021 and 7.7% uptake rate being offered in 2022 and 2023. Similarly, the percentage values are:				

Initiation boost (amount)	What is expected	Screening coverage predicted by the model		Interpretation of the results
		Observed	Expected	
0%	This is equivalent to No YouScreen	68.22%	68.12%	The model works as expected.
10%	Screening coverage is predicted to increase by 10% of size of the increase in the YouScreen (combined approach) scenario	68.85%	68.74%	The model works as expected.
20%	Screening coverage is predicted to increase by 20% of size of the increase in the YouScreen (combined approach) scenario	69.19%	69.37%	The model works as expected.
60%	Screening coverage is predicted to increase by 60% of size of the increase in the YouScreen (combined approach) scenario	71.95%	71.86%	The model works as expected.
100%	This is equivalent to YouScreen (combined approach)	74.44%	74.35%	The model works as expected.

Appendix 3: Schematics of screening initiation under No YouScreen (status quo) and YouScreen scenarios

We show two simplified schematics. In both, we assumed a cohort of 100 women born in 1995 (i.e. turning 26 in 2021) started entering screening when they were 25. It was also assumed there were 20% of women initiating screening every year, and by age of 64, there would have been 96%, based on ⁵, of women at least had one screen in their lifetime when there were no self-sampling offered as an intervention; See detail in Figure 22. ⁵ (National Health Service England 2022), of women at least had one screen in their lifetime when there were no self-sampling offered as an intervention; See detail in Figure 22. When the self-sampling was introduced, it was still assumed a 20% screening initiation uptake rate every year. In addition, we also assumed the self-sampling annual rate to be 7.7% and it was offered for three consecutive years. Moving down to future years, it was shown, in Figure 23, that the population of never screeners is smaller for YouScreen scenarios compared to No YouScreen scenario at the same of age. Also, it was demonstrated the screeners via clinician collected were reduced in No YouScreen scenario compared to YouScreen scenario. This is because they accepted the self-samplings hence were recruited in the self-sampling pathway and maintained on the pathway until they exited the screening entirely.

Figure 22 Schematic of screening initiation under No YouScreen scenario.

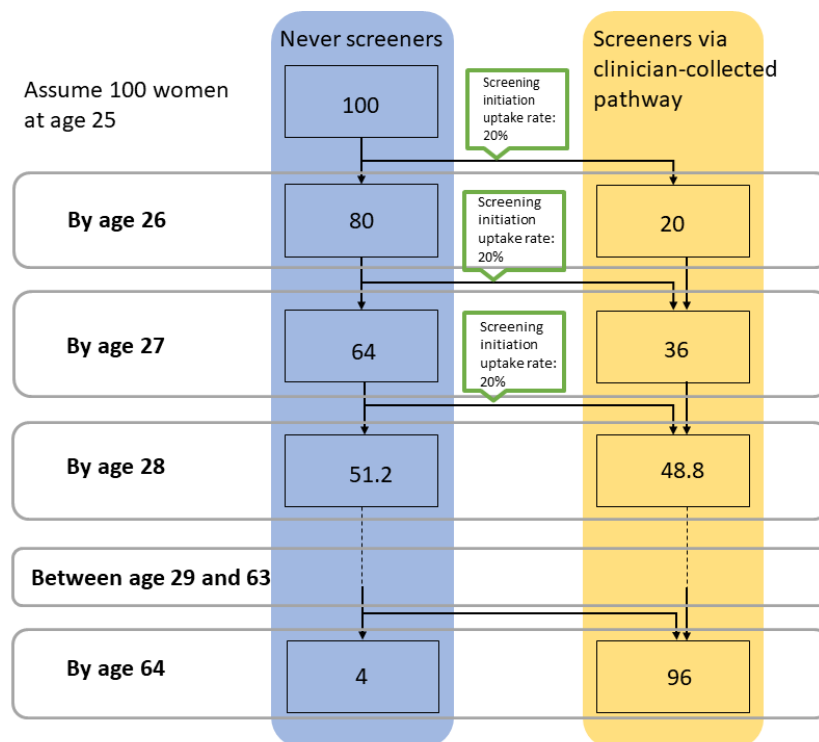
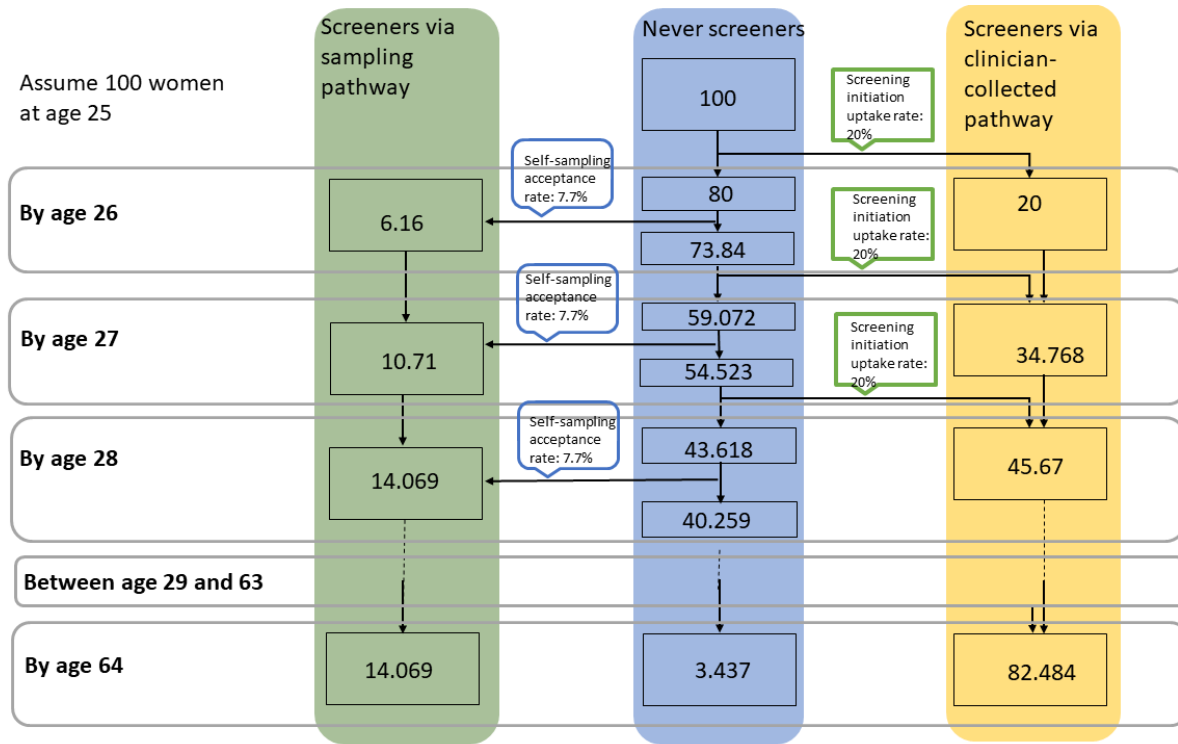


Figure 23 Schematic of screening initiation under YouScreen scenarios.



Appendix 4: Australian hysterectomy prevalence

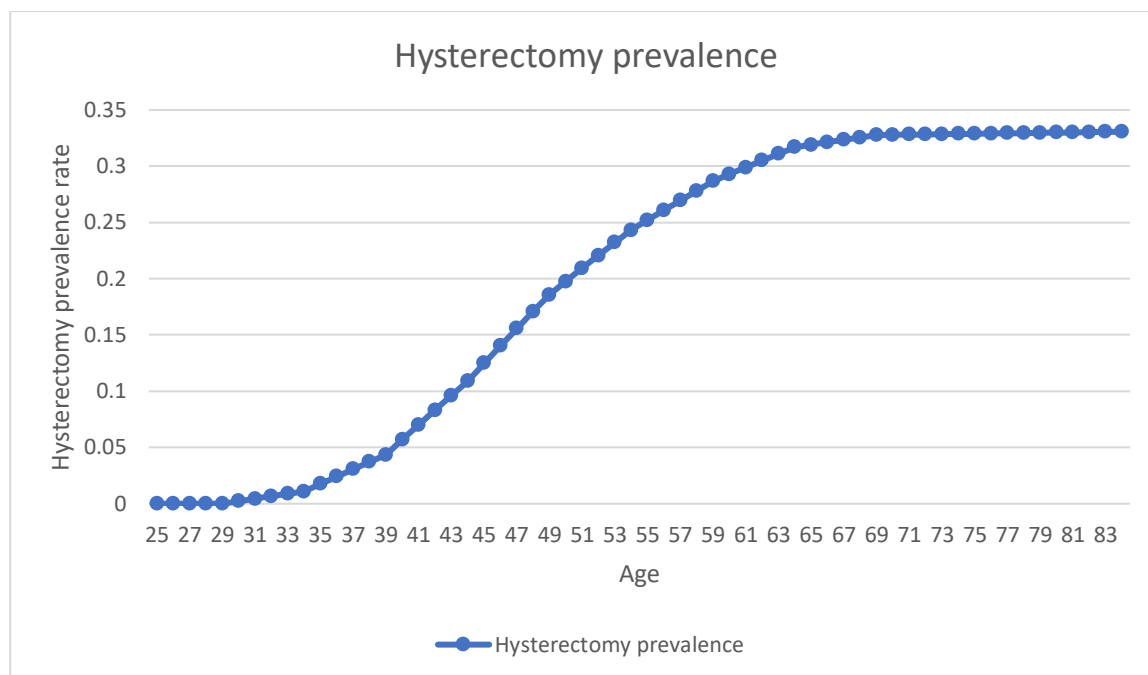


Figure 24 Australian hysterectomy prevalence. The age-specific probability of benign hysterectomy was derived from the 2001 and 2005 National Health Survey ^{41,42}

Glossary

Technical terms	Explanation
Adequate colposcopy	The cervix is clearly seen and not obscured by blood, inflammation or scarring.
ASC-H: atypical squamous cells, possible high-grade lesion	In the standard US Bethesda System, a category of atypical squamous cells, possible high-grade lesion, is equivalent to possible high-grade squamous intraepithelial lesion (pHSIL) in the Australian Modified Bethesda System.
ASC-US: atypical squamous cells, undetermined significance	In the standard US Bethesda System, a category of atypical squamous cells of undetermined significance: the nature of the abnormality is uncertain or unequivocal, is equivalent to possible low-grade squamous intraepithelial lesion (pLSIL) in the Australian Modified Bethesda System.
Biopsy	Removal of tissue for medical examination
CIN: Cervical Intraepithelial Neoplasia	Refers to abnormal changes in the cells on the surface of the cervix that are seen using a microscope (i.e. histologically confirmed).
CIN1	Mild dysplasia.
CIN2	Moderate dysplasia.
CIN3	Severe dysplasia to carcinoma in situ The term CIN2+ refers to CIN2,3, AIS or cervical cancer; CIN3+ refers to CIN3, AIS or cervical cancer.
CIN2/3	Refers to CIN2 or CIN3.
Clinician	Doctor, nurse or midwife involved in providing clinical cervical screening services.
Colposcopy	The examination of the cervix and vagina with a magnifying instrument called a colposcope, to check for abnormalities.
Colposcopists	Health professionals, usually gynaecologists, trained to perform colposcopy.
Confidence Interval (CI)	A way of expressing how certain we are about the findings from a study, using statistics. It gives a range of results that is likely to include the 'true' value for the population. A wide confidence interval (CI) indicates a lack of certainty about the true effect of the test or treatment - often because a small group of patients has been studied. A narrow CI indicates a more precise estimate (for example, if a large number of patients have been studied). The CI is usually stated as '95% CI', which means that the range of values has a 95 in 100 chance of including the 'true' value. For example, a study may state that 'based on our sample findings, we are 95% certain that the 'true' population blood pressure is not higher than 150 and not lower than 110'. In such a case the 95% CI would be 110 to 150.
Cost-effectiveness	A cost-effectiveness evaluation is a form of economic analysis that compares the relative gain in effectiveness and relative gain in costs of two or more possible scenarios.
Cost-Effectiveness Plane (CEP)	Represents differences in costs and health outcomes on a graph, with effectiveness on the x-axis and cost on the y-axis. The graph is divided into 4 'quadrants'. In the

	northeast quadrant, interventions are more effective and more costly (where most interventions lie). Southeast is less costly and more effective, southwest is less costly and less effective, and northwest is more costly and less effective.
Cost-Effectiveness Acceptability Curves (CEACs)	The cost-effectiveness acceptability curve (CEAC) is a graph summarising the impact of uncertainty on the result of an economic evaluation, frequently expressed as an ICER (incremental cost-effectiveness ratio) in relation to possible values of the cost-effectiveness threshold. The graph plots a range of cost-effectiveness thresholds on the horizontal axis against the probability that the intervention will be cost-effective at that threshold on the vertical axis.
Cost-Effectiveness Acceptability Frontier (CEAF)	A region on a plot that shows the probability that the technology with the highest expected net benefit is cost-effective.
Deterministic analysis	Considers the sensitivity of results based on set model inputs and considers the effect of uncertainty on the results
Discounted costs	A measure of the total predicted cost associated with cervical cancer screening for the lifetime of a woman, which is discounted by 3.5% per year since the medical intervention.
Discounted life years	A measure of the predicted probability of remaining alive each year after birth, which is discounted by 3.5% per year since the medical intervention.
Dominated	A treatment or intervention option that is both more expensive and results in poorer health outcomes than an alternative strategy is said to be 'dominated' by that alternative strategy.
Dysplasia	An abnormality of epithelial growth and differentiation, categorised as mild, moderate and severe, which correlates with CIN1, CIN2 and CIN3.
Dynamic model	A model that captures time-dependent changes in the state of the system, in contrast to a static model, which is time-independent. For instance, the change in the number of infected women over time due to vaccination may influence the rate of new infections due to herd immunity, and cannot be captured through a static model.
FIGO	The International Federation of Gynaecology and Obstetrics.
HPV	Human papillomavirus.
HPV (16/18):	A test result when HPV types 16 and or 18 are detected using routine HPV tests in a laboratory.
HPV (not 16/18):	A test result when only oncogenic HPV types other than 16 and/or 18 are detected using routine HPV tests in a laboratory.
HPV (any type)	Any oncogenic HPV types which are detected using routine HPV tests in a laboratory.
HPV detected	A pathology report where a HPV test result of any oncogenic HPV type has been detected by the HPV testing platform.
HPV not detected	A pathology report where oncogenic HPV types not detected by the HPV testing platform.
HPV test	A test for oncogenic HPV types (on either a clinician-collected sample or a self-collected sample).
hr-HPV type	HPV types associated with high risk of cervical high grade precancerous lesions.

HSIL	High-grade squamous intraepithelial lesion. In the Australian context, HSIL is used to refer to a cytology test which is predictive of a high-grade precancerous lesion (AMBS 2004), or histologically confirmed high grade precancerous lesion (HSIL-CIN2 or HSIL CIN3 as per LAST terminology).
Hysterectomy (total)	Complete surgical removal of the uterus including the cervix.
LBC: liquid-based cytology	A way of preparing cervical samples for examination in the laboratory.
LEEP	Loop electrosurgical excision procedure.
LLETZ	Large loop excision of the transformation zone.
LSIL	Low-grade squamous intraepithelial lesion. In the Australian context, LSIL is used to refer to a cytology predictive of a low-grade precancerous lesion (AMBS 2004), or histologically confirmed low grade precancerous lesion (LSIL-HPV, LSIL→ condyloma and LSIL-CIN1 as per LAST terminology).
Multiple-cohort model	A model used to simulate outcomes for cohorts born at different ages.
Negative colposcopy	A colposcopy in which no abnormalities are seen: it does not include the subsequent reports on any biopsy taken. Also called a 'normal' colposcopy and implies that the entire transformation zone of the cervix is visible.
Net Benefit and Net Monetary Benefit	The net benefit can be expressed in health (for example, using quality-adjusted life years [QALYs]) or monetary terms. The net health benefit is the difference between the total expected QALYs and the health expected to be forgone elsewhere (the total expected costs divided by the maximum acceptable incremental cost-effectiveness ratio [ICER] value). The net monetary benefit is the difference between the monetary value of total expected QALYs (expected QALYs multiplied by the maximum acceptable ICER value) and total expected costs.
Oncogenic HPV	potentially cancer-causing HPV DNA types, pathogenically linked to intraepithelial neoplasia, e.g. of the uterine cervix (termed CIN).
Oncogenic HPV types	Testing for subgroups of high risk HPV types e.g. types 16 or 18.
Parameter uncertainty	Uncertainty about the mean values of parameters (for example, health outcomes, utilities and resource use) included in the model.
pHSIL	possible HSIL in the Australian Modified Bethesda System – broadly equivalent to ASC-H in the US Bethesda system.
pLSIL	possible LSIL in the Australian Modified Bethesda System – broadly equivalent to ASCUS in US Bethesda system.
Probabilistic Sensitivity Analysis (PSA)	Probability distributions are assigned to the uncertain parameters and are incorporated into evaluation models based on decision analytical techniques (for example, Monte Carlo simulation).
Reflex LBC	reflex liquid-based cytology LBC (cytology) – a test performed on a liquid-based cytology sample after oncogenic HPV types have been detected. Reflex LBC may allow for the triage along different pathways: negative, LSIL and HSIL, or glandular.
Repeat HPV test	An HPV test performed after a previous unsatisfactory HPV test.

Self-sample	A lower vaginal sample that can be used to perform an HPV test. The lower vaginal sample could be collected by the patient, or the healthcare professional (if the patient has difficulty collecting the sample by themselves or prefers the provider to collect the sample using a self-collection swab without using a speculum). LBC cannot be performed on a self-collected sample.
Strongly dominated	Any strategy with lower effectiveness but higher costs than another strategy is said to be "strongly dominated".
Unvaccinated cohorts	Women and people with a cervix who were not age eligible HPV vaccination, and who experience no herd immunity effects from the natural HPV Vaccination Program.
Willingness to Pay (WTP)	The maximum amount that an economic agent is willing to pay to acquire a specified good or service. The willingness to pay is private information but may be obtained by using revealed preference techniques or the contingent valuation method.

References

1. Drysdale H, Waller J, Marlow L. Preferences for self-sampling in the context of a choice at the point of invitation for cervical screening. [Internet]. 2022 [cited 2023 Aug 2]. Available from: <https://osf.io/c54e8/>
2. Lim A. Evaluating the feasibility of offering HPV self-sampling kits to those who have not attended the NHS cervical screening programme in England [Internet]. 2020. Available from: <https://www.isrctn.com/ISRCTN12759467?q=Youscreen&filters=&sort=&offset=1&totalResults=1&page=1&pageSize=10>
3. Greater London Authority. Land Area and Population Density, Ward and Borough [Internet]. 2021. Available from: <https://www.data.gov.uk/dataset/a76f46f9-c10b-4fe7-82f6-aa928471fcd1/land-area-and-population-density-ward-and-borough>.
4. Office for National Statistics. Male and female populations [Internet]. 2023. Available from: [https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/male-and-female-populations/latest/#:~:text=The%20data%20shows%20that%3A,up%2029.2%20million%20\(49.0%25](https://www.ethnicity-facts-figures.service.gov.uk/uk-population-by-ethnicity/demographics/male-and-female-populations/latest/#:~:text=The%20data%20shows%20that%3A,up%2029.2%20million%20(49.0%25)
5. National Health Service England. Cervical Screening Programme, England - 2021-2022 [NS] [Internet]. 2022 [cited 2023 May 24]. Available from: <https://digital.nhs.uk/data-and-information/publications/statistical/cervical-screening-annual/england-2021-2022>
6. Brisson M, Kim JJ, Canfell K, Drolet M, Gingras G, Burger EA, et al. Impact of HPV vaccination and cervical screening on cervical cancer elimination: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet*. 2020 Feb 22;395(10224):575–90.
7. Canfell K, Kim JJ, Brisson M, Keane A, Simms KT, Caruana M, et al. Mortality impact of achieving WHO cervical cancer elimination targets: a comparative modelling analysis in 78 low-income and lower-middle-income countries. *Lancet*. 2020 Feb 22;395(10224):591–603.
8. Simms KT, Steinberg J, Caruana M, Smith MA, Lew JB, Soerjomataram I, et al. Impact of scaled up human papillomavirus vaccination and cervical screening and the potential for global elimination of cervical cancer in 181 countries, 2020-99: a modelling study. *Lancet Oncol*. 2019 Mar;20(3):394–407.
9. Burger EA, de Kok IMCM, Groene E, Killen J, Canfell K, Kulasingam S, et al. Estimating the Natural History of Cervical Carcinogenesis Using Simulation Models: A CISNET Comparative Analysis. *J Natl Cancer Inst*. 2020 Sep 1;112(9):955–63.
10. Hall MT, Smith MA, Lew JB, O’Hallahan J, Fentiman G, Neal H, et al. The combined impact of implementing HPV immunisation and primary HPV screening in New Zealand: Transitional and long-term benefits, costs and resource utilisation implications. *Gynecol Oncol*. 2019 Mar;152(3):472–9.
11. Smith MA, Gertig D, Hall M, Simms K, Lew JB, Malloy M, et al. Transitioning from cytology-based screening to HPV-based screening at longer intervals: implications for resource use. *BMC Health Services Research*. 2016 Apr 26;16(1):147.

12. Hall MT, Simms KT, Lew JB, Smith MA, Saville M, Canfell K. Projected future impact of HPV vaccination and primary HPV screening on cervical cancer rates from 2017–2035: Example from Australia. *PLOS ONE*. 2018;13(2):e0185332.
13. Simms KT, Keane A, Nguyen DTN, Caruana M, Hall MT, Lui G, et al. Benefits, harms and cost-effectiveness of cervical screening, triage and treatment strategies for women in the general population. *Nature Medicine*. 2023 Dec 1;29(12):3050–8.
14. United Nations Department of Economic and Social Affairs. “Mortality data.” *World Population Prospects* [Internet]. 2019 [cited 2022 Jun 16]. Available from: [https://population.un.org/wpp/Download/Files/1_Indicators%20\(Standard\)/EXCEL_FILES/3_Mortality/WPP2019_MORT_F17_3_ABRIDGED_LIFE_TABLE_FEMALE.xlsx](https://population.un.org/wpp/Download/Files/1_Indicators%20(Standard)/EXCEL_FILES/3_Mortality/WPP2019_MORT_F17_3_ABRIDGED_LIFE_TABLE_FEMALE.xlsx).
15. Green LI, Mathews CS, Waller J, Kitchener H, Rebolj M, HPV Pilot Steering Committee. Attendance at early recall and colposcopy in routine cervical screening with human papillomavirus testing. *Int J Cancer*. 2021 Apr 15;148(8):1850–7.
16. Wagner K, White J, Saliba V. Human Papillomavirus (HPV) Vaccine Coverage in England, 2008/09 to 2013/14. A review of the full six years of the three-dose schedule. [Internet]. 2015 [cited 2022 Nov 28]. Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/774074/HPV_Vaccine_Coverage_in_England_200809_to_201314.pdf
17. Rai Y, Webster H, Tessier E, White J, Saliba V. Human papillomavirus (HPV) vaccination coverage in adolescent females and males in England: academic year 2019 to 2020 [Internet]. 2020 [cited 2022 Nov 28]. (Health Protection Report Volume 14 Number 19). Available from: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/927694/hpr1920_HPVCVC.pdf.
18. Bains I, Choi YH, Soldan K, Jit M. Clinical impact and cost-effectiveness of primary cytology versus human papillomavirus testing for cervical cancer screening in England. *Int J Gynecol Cancer*. 2019 May 1;29(4):669.
19. Simms KT, Smith MA, Lew JB, Kitchener HC, Castle PE, Canfell K. Will cervical screening remain cost-effective in women offered the next generation nonavalent HPV vaccine? Results for four developed countries. *Int J Cancer*. 2016 Dec 15;139(12):2771–80.
20. Simonella L, Howard K, Canfell K. A survey of population-based utility scores for cervical cancer prevention. *BMC Res Notes*. 2014;7:899.
21. Drolet M, Brisson M, Maunsell E, Franco EL, Coutlee F, Ferenczy A, et al. The psychosocial impact of an abnormal cervical smear result. *Psychooncology*. 2012;21(10):1071–81.
22. Gold MR, Franks P, McCoy KI, Fryback DG. Toward consistency in cost-utility analyses: using national measures to create condition-specific values. *Med Care*. 1998;36(6):778–92.
23. Kim JJ, Wright TC, Goldie SJ. Cost-effectiveness of alternative triage strategies for atypical squamous cells of undetermined significance. *JAMA JID - 7501160*. 2002;287(18):2382–90.

24. Myers ER, Green S, Lipkus I. Patient preferences for health states related to HPV infection: visual analogue scales vs time trade-off elicitation. *Proceedings of the 21st International Papillomavirus Conference*. Proceedings of the 21st International Papillomavirus Conference; 2004; Mexico City, Mexico.
25. Elbasha EH, Dasbach EJ, Insinga RP. Model for assessing human papillomavirus vaccination strategies. *Emerg Infect Dis*. 2007;13(1):28–41.
26. Briggs AH, Weinstein MC, Fenwick EAL, Karnon J, Sculpher MJ, Paltiel AD, et al. Model parameter estimation and uncertainty analysis: a report of the ISPOR-SMDM Modeling Good Research Practices Task Force Working Group-6. *Med Decis Making*. 2012;32(5):722–32.
27. National Institute for Health and Care Excellence. Developing NICE guidelines: the manual [Internet]. 2014. Available from: <https://www.nice.org.uk/process/pmg20>
28. Barr HK, Guggenbickler AM, Hoch JS, Dewa CS. Real-World Cost-Effectiveness Analysis: How Much Uncertainty Is in the Results? *Curr Oncol*. 2023 Apr 7;30(4):4078–93.
29. Hatzwell AJ, Bullement A, Briggs A, Paulden M, Stevenson MD. Probabilistic Sensitivity Analysis in Cost-Effectiveness Models: Determining Model Convergence in Cohort Models. *Pharmacoeconomics*. 2018 Dec;36(12):1421–6.
30. van Hout BA, Al MJ, Gordon GS, Rutten FF. Costs, effects and C/E-ratios alongside a clinical trial. *Health Econ*. 1994;3(5):309–19.
31. Briggs AH, Claxton K, Sculpher MJ. *Decision modelling for health economic evaluation*. Oxford University Press; 2006. (Oxford handbooks in health economic evaluation).
32. National Institute for Health and Care Excellence. NICE process and methods [Internet]. 2024 [cited 2024 Jan 6]. Available from: <https://www.nice.org.uk/process/pmg20>
33. Claxton K. Exploring uncertainty in cost-effectiveness analysis. *Pharmacoeconomics*. 2008;26(9):781–98.
34. Barton GR, Briggs AH, Fenwick EAL. Optimal cost-effectiveness decisions: the role of the cost-effectiveness acceptability curve (CEAC), the cost-effectiveness acceptability frontier (CEAF), and the expected value of perfection information (EVPI). *Value Health*. 2008;11(5):886–97.
35. Fenwick E, Claxton K, Sculpher M. Representing uncertainty: the role of cost-effectiveness acceptability curves. *Health Econ*. 2001 Dec;10(8):779–87.
36. Sculpher M, Claxton K. Establishing the cost-effectiveness of new pharmaceuticals under conditions of uncertainty--when is there sufficient evidence? *Value Health*. 2005;8(4):433–46.
37. McCredie MR, Sharples KJ, Paul C, Baranyai J, Medley G, Jones RW, et al. Natural history of cervical neoplasia and risk of invasive cancer in women with cervical intraepithelial neoplasia 3: a retrospective cohort study. *Lancet Oncology*. 2008;9(5):425–34.
38. Landy R, Windridge P, Gillman MS, Sasieni PD. What cervical screening is appropriate for women who have been vaccinated against high risk HPV? A simulation study. *Int J Cancer*. 2018 Feb 15;142(4):709–18.

39. Public Health England. Cervical screening: care pathway [Internet]. 2021 [cited 2023 Oct 1]. (NHS cervical screening (CSP) programme). Available from: <https://www.gov.uk/government/publications/cervical-screening-care-pathway/cervical-screening-care-pathway>
40. Public Health England. Cervical screening: invasive cervical cancer audit 2013 to 2016 [Internet]. 2019 [cited 2023 Feb 19]. Available from: <https://www.gov.uk/government/publications/cervical-screening-invasive-cervical-cancer-audit-2013-to-2016>
41. Australian Bureau of Statistics. National Health Survey, Summary of Results, Australia, 2001. Canberra, Australia; 2002. Report No.: Cat. No. 4364.0.
42. Australian Bureau of Statistics. National Health Survey, Summary of Results, Australia, 2004-05. Canberra, Australia; 2006. Report No.: Cat. No. 4364.0.