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Two self-sampling strategies for HPV primary cervical cancer screening compared with clinician-collected sampling: an economic evaluation

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ABSTRACT

Objective To compare the costs and effects of three sampling strategies for human papillomavirus (HPV) primary screening.

Design Cost-consequence analysis from a health system perspective using a deterministic decision tree model.

Setting England.

Participants A cohort of 10 000 women aged 25–65 years eligible for the National Health Service Cervical Screening Programme (NHSCSP).

Methods The model was based on the NHSCSP HPV primary screening pathway and adapted for self-sampling. It used a 3-year cycle: routine screening (year 1) and recall screening (years 2/3). Parameter inputs were informed using published studies, NHSCSP reports and input from experts and manufacturers. Costs were from 2020/2021, British pound sterling (£).

Interventions Three sampling strategies were implemented: (1) routine clinician-collected cervical sample, (2) self-collected first-void (FV) urine, (3) self-collected vaginal swab. The hypothetical self-sampling strategies involved mailing women a sampling kit.

Main outcome measures Primary outcomes: overall costs (for all screening steps to colposcopy), number of complete screens and cost per complete screen. Secondary outcomes: number of women screened, number of women lost to follow-up, cost per colposcopy and total screening costs for a plausible range of uptake scenarios.

Results In the base case, the average cost per complete screen was £56.81 for clinician-collected cervical sampling, £38.57 for FV urine self-sampling and £40.37 for vaginal self-sampling. In deterministic sensitivity analysis, the variables most affecting the average cost per screen were the cost of sample collection for clinician-collected sampling and the cost of laboratory HPV testing for the self-sampling strategies. Scaled to consider routine HPV testing in England, if uptake in non-attenders increased by 15% and 50% of current screeners converted to self-sampling, the NHSCSP would save £19.2 million (£V urine) or £16.5 million (vaginal) per year.

Conclusion Self-sampling could provide a less costly alternative to clinician-collected sampling for routine HPV primary screening and offers opportunities to expand the reach of cervical screening to under-screened women.

INTRODUCTION

Cervical cancer is a leading cause of mortality among women worldwide but can be prevented through screening for high-risk human papillomavirus (HR-HPV).1–3 HPV-positive samples are triaged by cytology to identify women at risk of high-grade cervical intraepithelial neoplasia (CIN2+) and treat them to prevent progression to cancer. The impact of cervical screening programmes is heavily dependent on achieving high participation rates.4 Screening uptake in England fell from 76% in 2010/2011 to 72% in 2019/2020, decreasing further during the COVID-19 pandemic to 70% in 2020/2021 when there were disruptions to the health service and in-person appointments were minimised.1,4–6

In England and many other countries, screening requires attendance at a healthcare facility where a healthcare professional
collects a cervical sample.\textsuperscript{7} Reported reasons for non-attendance include difficulty making an appointment, embarrassment, fear and inconvenience.\textsuperscript{8, 9} There has been a growing interest in the use of vaginal self-sampling for HR-HPV testing due to its relative convenience and acceptability among women.\textsuperscript{10-13} Home self-sampling is successfully used in other screening programmes, for example, bowel cancer\textsuperscript{14} and chlamydia\textsuperscript{15} and for some other sexually transmitted infections.\textsuperscript{16} Countries, including Australia, Denmark, Malaysia and the Netherlands, have or are moving to self-sampling as a screening option.\textsuperscript{17-19} In 2021, National Health Service (NHS) England launched YouScreen, a pilot study in targeted locations offering vaginal self-sampling kits to individuals overdue for screening.\textsuperscript{20}

Self-collected first void (FV) urine is another option for HPV screening.\textsuperscript{10, 21, 22} There is growing evidence that if HR-HPV assays are optimised for use on urine or self-collected vaginal samples, their diagnostic performance is non inferior to that achieved for clinician-collected cervical samples.\textsuperscript{23-25} Currently, within the NHS Cervical Screening Programme (NHSCSP), cytology is performed on HR-HPV-positive samples to determine whether colposcopy is required. Cytology cannot be performed on urine or vaginal swab samples, so an HR-HPV positive result means a second, clinician-collected sample is required. Despite this additional step, which might be avoidable with new technologies,\textsuperscript{26} self-sampling is likely to be cost-saving and remove barriers to screening. It has the potential to increase uptake in those who do not currently screen, referred to as non-attenders, and improve user experience and choice.\textsuperscript{27, 28}

This study aimed to compare the cost of cervical screening (including sample collection, HPV testing, cytology and colposcopy) using three sampling strategies: clinician-collected cervical sampling, FV urine self-sampling and vaginal self-sampling. Scenarios were explored using different uptake rates and offering self-sampling to everyone or only to non-attenders. The results will inform decision-makers about the screening costs and effects on the number of complete screens and colposcopies if self-sampling were offered as an alternative to routine screening in HPV primary cervical screening programmes.

### METHODS

#### Model type and structure

A deterministic decision tree model was constructed in Excel V.2202 (Microsoft, Redmond, Washington, USA) to simulate a hypothetical cohort of 10,000 people invited for screening. The model’s structure was based on the HPV primary screening algorithm for cervical cancer screening used in England (see box 1) and many other countries (figure 1) and based on a previous model.\textsuperscript{29, 30}

#### Box 1 Screening eligibility in England’s NHSCSP

In England, women and people with a cervix aged 25–64 years are eligible for cervical screening every 3 years (for those aged 25–49 years) or every 5 years (for those aged 50–64 years). Invitations to screen as part of the NHSCSP are automatically sent to anyone registered with a general practice (GP) as female. People with a cervix who are registered as male are not automatically sent an invite (due to limitations of the information technology system currently used) but should receive an invite sent by their GP or healthcare teams managing gender reassignment and can request screening themselves.

We refer to people in our model cohort as ‘women’ reflecting the reality of the current system and acknowledging that some people with a cervix who are not registered as a woman might be missed despite being eligible for cervical screening.

NHSCSP, National Health Service Cervical Screening Programme.

#### Comparators

A cost-consequence analysis from a health system perspective was performed to compare three sampling strategies within the context of the NHSCSP: clinician-collected cervical sampling (standard of care, SoC), FV urine self-sampling and vaginal swab self-sampling. In the base case, eligibility for screening (box 1) and screening uptake (attendance in primary care for clinician-collected sampling or return of sample by post) was the same for all strategies (online supplemental table 1). It was assumed that there was equivalent HPV test sensitivity and specificity for each sample type.

The self-sampling strategies were chosen because they are acceptable to patients and are already used for home testing in other disease areas. The Colli-Pee device (Novosanis, Wijnegem, Belgium)\textsuperscript{31} collects a standardised volume of FV urine without the need for the person to interrupt the flow of urine. The use of a standard urine pot was not assessed, since testing mid/random flow urine for HPV is not as accurate as testing FV urine.\textsuperscript{32}

#### Time horizon

The model considered a 3-year time horizon. This period includes the minimum time before recall to routine screening and includes the complete cycle of events for HR-HPV-positive women with normal cytology in years 1 and 2 (figure 1). No long-term outcomes or costs associated with cancer diagnosis or treatment were considered.

#### Current cervical screening pathway

At present, within the NHSCSP (figure 1), people eligible for screening are invited by letter to attend an appointment at their general practice (GP) during which a cervical sample is taken by a clinician. The sample is sent to one of eight laboratories where it is tested for HR-HPV. Women who are HR-HPV-negative are discharged to routine recall. HR-HPV-positive samples are tested for abnormal cell changes using liquid-based cytology. Women with normal cytology are recalled for a repeat screen the following year, while those with abnormal cytology are referred for colposcopy. Women recalled in year 2 follow
the same pattern as year 1. Anyone HR-HPV positive in year 3 is referred for colposcopy. The model included the cost of sample collection, HPV testing, cytology and colposcopy (where needed) for routine screening in year 1 and recall screening in years 2 and 3.

**Self-screening strategies**

An opt-in rather than an opt-out strategy was assessed, individuals being invited to screen via letter with acceptance via an app or website (eg, the NHS England app). Those who accept receive a self-sampling kit in the mail containing the Colli-Pee device (Strategy 2) or the FLOQSwab (COPAN Diagnostics, Brescia, Italy) (Strategy 3) plus instructions and a return Freepost envelope. Using the standard postal service, the sample is sent to a laboratory for HR-HPV testing. As in SoC, HR-HPV-negative women are discharged to routine recall. Anyone HR-HPV positive is invited for cervical sampling so that cytology can be performed. This second sample is not tested for HPV. As in SoC, HR-HPV-positive individuals with normal cytology are recalled for follow-up or referred for colposcopy (if in year 2). Recall testing in years 2–3 is via self-sampling, followed by clinician-collected cervical sampling if HR-HPV positive.

**Outcomes**

The primary outcomes assessed were the overall screening costs, the number of complete screens and the average cost per complete screen (calculated as the total cost divided by the number of complete screens). A complete screen refers to either an HPV negative result or an HPV positive result with cytology and colposcopy or recall in years 2–3 where required.

The secondary outcomes assessed were the number of women screened, the number lost to follow-up (LTFU) and the cost per colposcopy (calculated as the total cost divided by the number of colposcopies). Each outcome was calculated for the complete 3-year screening cycle.

In scenario analyses, the total cost using each of the sampling strategies was calculated using the number of women invited to routine screening in the NHSCSP in 2020/2021.

**Population**

The same hypothetical cohort of 10000 individuals was used for each sampling strategy. Data on HPV positivity, cytology and colposcopy were taken from the NHSCSP and a pilot study of 403883 women screened in England. Age-specific data from the study were
adapted to reflect the national age distribution of people screened in the NHSCSP (online supplemental tables 2–6). Since there are limited data to inform HPV positivity estimates in people who do not regularly screen, it was assumed that non-attenders had the same prevalence of HPV and abnormal cytology as attenders.

Cost
Costs included: screening invite letter (including postage), sample collection in primary care, self-sample collection kit including instructions and return envelope, postage of self-collection kits and return of samples, laboratory HPV testing, cytology and colposcopy (table 1 and online supplemental tables 7–12). Unit costs (presented in £) were informed using published studies, NHS tariffs, Royal Mail postal charges, quotes from manufacturers or estimated where necessary.

Where required, costs were inflated to 2020/2021 prices using the NHS Cost Inflation Index. A discount rate of 3.5% was applied to costs incurred in years 2/3 (figure 1). The cost of HPV testing for vaginal swabs or urine samples was adapted from the cost of testing cervical samples used in a published economic evaluation to account for changes in the staff time and consumables required (online supplemental table 12). These calculations were informed by published HPV assay protocols and with input from a lead scientist at one of the laboratories providing HPV testing for the NHSCSP. It was assumed that high-throughput testing platforms compatible with the tubes used for self-collection of urine samples would be used for laboratory HPV testing (see online supplemental table 12).

For the self-sampling strategies, the model included the cost of self-sampling kits requested and sent but not used in year 1 but did not include the cost of unused kits in years 2/3. For SoC, the cost of non-attendance at booked appointments in primary care (for any year) was not included. The cost of an app or website used to select self-sampling was not included in the model, nor was the cost of a reminder letter for non-responders, costs related to training or changes to laboratory equipment or costs for the administration or coordination of the NHSCSP.

Probability inputs
Data from an English pilot study were used to inform HPV positivity in years 1–3, age weighted to represent the national age distribution of individuals screening within the NHSCSP in 2020–2021 (online supplemental tables 2–4). The same probabilities for HPV positivity were used for each sampling strategy since there is growing evidence that assays optimised for use on FV urine or vaginal swabs are non-inferior to existing assays used on clinician-collected cervical samples and therefore, it was assumed that HPV assays for each sample type had equivalent performance.

The probability of LTFU at colposcopy and at HPV recall was informed by NHSCSP data over the period 2017–2020. The chance of attending for clinician-collected sampling following a positive HPV result was the same for both self-sampling strategies and informed by published studies.

Screening uptake was based on NHSCSP 2017–2020 data (online supplemental table 1) and the same for each sampling strategy. The probability of booking an appointment (strategy 1) or requesting a self-sampling kit (strategies 2 and 3) was back-calculated to account for a 12% non-attendance or non-return of samples.

Deterministic sensitivity analysis
A one-way deterministic sensitivity analysis (DSA) was performed to assess the impact of varying each parameter on the cost per complete screen. High and low values for costs and probabilities were informed by published studies or varied by ±10% or ±20% the baseline value. Due to uncertainty around the cost of cytology, +100% the baseline value was used for the high value.

Scenario analysis
In scenario analyses, the total cost of the NHSCSP was calculated for each sampling strategy using a population of 4039982, representing the number of people invited to routine screening in 2020/2021. Costs were also calculated for scenarios where the choice of self-sampling was offered to everyone or only to non-attenders and where the uptake was held constant or increased, combined with different levels of conversion to self-sampling, informed by studies predominantly focused on self-sampling offered to non-attenders (online supplemental table 13). Additional scenarios were used to assess the impact of a lower HPV positivity, that is, in an HPV-vaccinated cohort, and a higher HPV positivity, as might be anticipated in some non-attender groups.

Patient and public involvement
‘Non-invasive cervical screening’ was identified as an important unmet research need according to patients and clinicians in a recent James Lind Alliance Detecting Cancer Early Priority Setting Partnership. A survey of more than 2000 women found that 80% prefer non-invasive screening, rising to 88% among current non-attenders. While urine self-sampling may offer a ‘major breakthrough’ to ‘end smear fear’, a formal cost evaluation is required to inform its implementation. Results from this study will be disseminated via social media and Jo’s Cervical Cancer Trust website.

RESULTS
Base case results
The primary and secondary outcomes of the three sampling strategies are presented in table 2. For the cohort of 10000 women offered screening, the cost per complete screen was £56.81 for SoC, compared with £38.57 for FV urine sampling and £40.37 for vaginal self-sampling. Compared with SoC, this results in a cost-saving
### Table 1  Base case model input parameters and the high and low values used in the one-way deterministic sensitivity analysis

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline value</th>
<th>Low value</th>
<th>High value</th>
<th>Reference/comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cost data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sampling strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Invitation to screen</td>
<td>£0.42</td>
<td>£0.34</td>
<td>£0.50</td>
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</tr>
<tr>
<td>Cytology</td>
<td>£9.06</td>
<td>£7.25</td>
<td>£18.12</td>
<td>Online supplemental table 76 75</td>
</tr>
<tr>
<td>Colposcopy*</td>
<td>£205.63</td>
<td>£164.50</td>
<td>£246.76</td>
<td>Online supplemental table 84 75</td>
</tr>
<tr>
<td>Discount rate</td>
<td>3.5%</td>
<td>0%</td>
<td>5%</td>
<td>Standard rate recommended by NICE46</td>
</tr>
<tr>
<td><strong>Clinic-collected cervical sampling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sample collection</td>
<td>£26.67</td>
<td>£21.33</td>
<td>£32.00</td>
<td>Online supplemental table 94 77 78</td>
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<tr>
<td>HPV testing</td>
<td>£15.86</td>
<td>£12.69</td>
<td>£19.03</td>
<td>Online supplemental table 1279</td>
</tr>
<tr>
<td><strong>FV urine self-sampling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-sample kit (including postage to individual)</td>
<td>£6.23</td>
<td>£4.98</td>
<td>£7.48</td>
<td>Estimate provided by Novosanis,† online supplemental table 10</td>
</tr>
<tr>
<td>Return postage of sample to laboratory</td>
<td>£1.07</td>
<td>£0.86</td>
<td>£1.28</td>
<td>Online supplemental table 1080</td>
</tr>
<tr>
<td>HPV testing</td>
<td>£15.67</td>
<td>£12.54</td>
<td>£18.81</td>
<td>Online supplemental table 1279</td>
</tr>
<tr>
<td><strong>Vaginal self-sampling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Self-sample kit (including postage to individual)</td>
<td>£3.61</td>
<td>£2.89</td>
<td>£4.33</td>
<td>Online supplemental table 114 81</td>
</tr>
<tr>
<td>Return postage of sample to laboratory</td>
<td>£1.07</td>
<td>£0.86</td>
<td>£1.28</td>
<td>Online supplemental table 1180</td>
</tr>
<tr>
<td>HPV testing</td>
<td>£20.25</td>
<td>£15.63</td>
<td>£24.87</td>
<td>Online supplemental table 1179</td>
</tr>
<tr>
<td><strong>Probabilities (for women aged 25–65 years)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All sampling strategies</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uptake at invitation</td>
<td>0.8191</td>
<td>0.6553</td>
<td>0.9829</td>
<td>Calculated value‡</td>
</tr>
<tr>
<td>HR-HPV positive result (year 1)</td>
<td>0.1155</td>
<td>0.0924</td>
<td>0.1386</td>
<td>Online supplemental table 3</td>
</tr>
<tr>
<td>HR-HPV positive result (year 2)</td>
<td>0.5647</td>
<td>0.4518</td>
<td>0.6777</td>
<td>Online supplemental table 46 36 36</td>
</tr>
<tr>
<td>HR-HPV positive result (year 3)</td>
<td>0.6578</td>
<td>0.5263</td>
<td>0.7894</td>
<td>Online supplemental table 46 36</td>
</tr>
<tr>
<td>Cytology abnormal (year 1)</td>
<td>0.2759</td>
<td>0.2207</td>
<td>0.3311</td>
<td>Online supplemental tables 5 and 66 36</td>
</tr>
<tr>
<td>Cytology abnormal (year 2)</td>
<td>0.1866</td>
<td>0.1492</td>
<td>0.2239</td>
<td>Online supplemental tables 5 and 66 36</td>
</tr>
<tr>
<td>LTFU at HPV recall (years 2/3)</td>
<td>0.4464</td>
<td>0.3571</td>
<td>0.5356</td>
<td>NHSCSP average value for 2017–20206</td>
</tr>
<tr>
<td>LTFU at referral to colposcopy</td>
<td>0.2520</td>
<td>0.2268</td>
<td>0.2772</td>
<td>NHSCSP average value for 2017–20206</td>
</tr>
<tr>
<td><strong>Clinic-collected cervical sampling</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does not attend booked appointment</td>
<td>0.1210</td>
<td>0.0968</td>
<td>0.5046</td>
<td>Assumption based on 12% non-attendance at booked appointments in primary care43</td>
</tr>
<tr>
<td>FV urine self-sampling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does not return sample</td>
<td>0.1210</td>
<td>0.0968</td>
<td>0.3554</td>
<td>Assumption§</td>
</tr>
<tr>
<td>Attends for recall cervical sample following positive HPV result (year 1 or 2)</td>
<td>0.9120</td>
<td>0.7931</td>
<td>1.000</td>
<td>4 42</td>
</tr>
<tr>
<td>Vaginal self-sampling</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Does not return sample</td>
<td>0.1210</td>
<td>0.0968</td>
<td>0.3554</td>
<td>Assumption§</td>
</tr>
<tr>
<td>Attends for recall cervical sample following positive HPV result (year 1 or 2)</td>
<td>0.9120</td>
<td>0.7931</td>
<td>1.000</td>
<td>4 42</td>
</tr>
</tbody>
</table>

*Weighted by the proportion with and without biopsy (online supplemental table 8).
†Cost is dependent on the number of devices purchased.
‡Back-calculated based on 72% uptake of screening in NHSCSP in 2017–2020 (online supplemental table 1) and 12% non-attendance in individuals who book primary care appointments.43
§Based on 12% non-attendance at booked appointments in primary care.
FV, first-void; HR-HPV, high-risk human papillomavirus; LTFU, lost to follow-up; NHSCSP, National Health Service Cervical Screening Programme; NICE, National Institute for Health and Care Excellence.
of £18.24 (32%) per completed screen for FV urine and £16.44 (28%) for vaginal self-sampling.

Since there are more steps in the self-sampling strategies (because HR-HPV-positive women must return to provide a sample for cytology), more people were LTFU than in SoC (n=462 vs n=418, respectively) and fewer women had a colposcopy. Using the base case values for attendance and LTFU, screening uptake would need to be 81% in the self-sampling strategies for the same number of women to have colposcopy in each strategy. At this uptake, the total screening costs for the cohort were £291,807 for FV urine sampling and £305,451 for vaginal sampling, and the cost per complete screen was £38.50 for FV urine sampling and £40.30 for vaginal sampling.

**Sensitivity analysis**

DSA was performed for each sampling strategy. Parameters with the most effect on the cost per complete screen are presented in figure 2. For all three sampling strategies, the cost of HPV testing, the cost of colposcopy and the probability of HPV positivity had a large effect on the cost per complete screen. In SoC, the cost of sample collection had the greatest effect when altered and for the self-sampling strategies, the probability of not returning a sample was important.

**Scenario analysis**

Several scenarios were assessed (table 3 and online supplemental tables 13 and 14). Using the number of people invited to routine screening in 2020/2021, the total cost for each sampling strategy (assuming the same uptake, scenario 1) for the 4,039,982 people offered screening would be £155,658,155 for SoC, £104,990,567 for FV urine sampling and £109,890,829 for vaginal self-sampling.

Offering self-sampling to non-attenders (scenario 3) would result in a cost of £56.26 per complete screen for FV urine and £56.32 for vaginal self-sampling (with 8% uptake), less than in SoC (£56.81). Although the cost per test was less for self-sampling than for SoC, the overall cost of the NHSCSP would increase if offering self-sampling meant that the overall uptake increased, and the amount of clinician-collected sampling was unchanged (scenario 3). If there was no change in uptake but some people opted for self-sampling instead of clinician-collected sampling, then the overall cost would fall but, due to the additional steps in the self-sampling pathway (in our current model), the total number with a complete screen would also fall (scenario 2). Scenario 4 had a more favourable outcome where the offer of self-sampling resulting in 15% uptake in non-attenders plus some conversion to self-sampling in attenders. With 50% conversion (scenario 4a, informed by a recent preference study in England[47]), the overall number receiving a complete screen would be higher than in SoC and save £19.2 million (FV urine) or £16.5 million (vaginal self-sampling) over the 3-year screening cycle for this cohort of 4 million women.

In England, HPV vaccination has been offered to girls of age 12–13 years since September 2008. As such, the first cohort of vaccinated girls is now eligible for the NHSCSP. A recent study found a 23% decrease in HPV positivity in 2018 in a cohort in which 55% had received three doses of the bivalent HPV vaccine, compared with a same-aged cohort in 2013 with 0% vaccinated.[48] If HPV positivity was 23.1% lower at baseline and the year 2 and year 3 recall (online supplemental table 15), the cost per complete screen would be £52.72 for SoC, £34.43 for

### Table 2 Baseline results for comparison of three sampling strategies for cervical cancer screening

<table>
<thead>
<tr>
<th>Outcomes for a cohort of 10,000 women aged 25–64 over a 3-year screening cycle</th>
<th>Clinician-collected sampling</th>
<th>FV urine self-sampling</th>
<th>Vaginal self-sampling</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of complete screens (%)</td>
<td>6782 (67.8)</td>
<td>6738 (67.4)</td>
<td>6738 (67.4)</td>
</tr>
<tr>
<td>Number attending for cervical sampling (%)</td>
<td>7618 (76.2)</td>
<td>915 (9.2)</td>
<td>915 (9.2)</td>
</tr>
<tr>
<td>Number of LTFU (%)</td>
<td>418 (4.2)</td>
<td>462 (4.6)</td>
<td>462 (4.6)</td>
</tr>
<tr>
<td>Number who have a colposcopy (%)</td>
<td>240 (2.4)</td>
<td>213 (2.1)</td>
<td>213 (2.1)</td>
</tr>
<tr>
<td>Total screening costs</td>
<td>£385,294</td>
<td>£259,879</td>
<td>£272,008</td>
</tr>
<tr>
<td>Costs related to sampling*</td>
<td>£207,067</td>
<td>£89,970</td>
<td>£67,528</td>
</tr>
<tr>
<td>Costs related to laboratory testing†</td>
<td>£129,708</td>
<td>£126,722</td>
<td>£161,293</td>
</tr>
<tr>
<td>Cost per complete screen‡</td>
<td>£56.81</td>
<td>£38.57</td>
<td>£40.37</td>
</tr>
<tr>
<td>Cost per person having colposcopy§</td>
<td>£160.8</td>
<td>£122.0</td>
<td>£127.7</td>
</tr>
</tbody>
</table>

Complete screen refers to either an HPV negative result or an HPV positive result with cytology and colposcopy where required plus recall in years 2–3 where required.

LTFU refers to those who receive a positive HPV result but do not attend for further investigations.

*Includes costs for screening invite, sample collection, self-sampling kits and kit postage.

†Includes costs for laboratory HPV testing and cytology.

‡Calculated as the total cost of screening divided by the number of complete screens.

§Calculated as the total cost of screening divided by the number of colposcopies.

FV, first-void; HPV, human papillomavirus; LTFU, lost to follow-up.
Figure 2  Effect of key variables on the cost per complete screen (£) for each sampling strategy. HR-HPV, high-risk human papillomavirus; LBC, liquid-based cytology.
<table>
<thead>
<tr>
<th>Scenario</th>
<th>Description</th>
<th>Overall uptake (%)</th>
<th>Total screening costs (£)</th>
<th>Complete screens (n)</th>
<th>Cost per complete screen* (£)</th>
<th>Colposcopies (n)</th>
<th>Cost per person having colposcopy† (£)</th>
<th>Cost-saving per complete screen compared with SoC (£)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scenario 1: replace one form of testing with another—no change in overall uptake</td>
<td>SoC</td>
<td>Only routine screening offered</td>
<td>72.0</td>
<td>155,658,155</td>
<td>2,739,987</td>
<td>56.81</td>
<td>96,084</td>
<td>1,608</td>
</tr>
<tr>
<td>1a FV urine</td>
<td>Only self-sampling offered</td>
<td>72.0</td>
<td>104,990,567</td>
<td>2,722,134</td>
<td>38.57</td>
<td>86,080</td>
<td>1,220</td>
<td>18.24</td>
</tr>
<tr>
<td>1b Vaginal</td>
<td>Only self-sampling offered</td>
<td>72.0</td>
<td>109,890,829</td>
<td>2,722,134</td>
<td>40.37</td>
<td>86,080</td>
<td>1,277</td>
<td>16.44</td>
</tr>
<tr>
<td>Scenario 2: self-sampling is offered as an option to all—no change in uptake in non-attenders</td>
<td>2a FV urine</td>
<td>Low conversion (25%) to self-sampling</td>
<td>72.0</td>
<td>142,991,258</td>
<td>2,735,524</td>
<td>52.27</td>
<td>94,123</td>
<td>1,519</td>
</tr>
<tr>
<td>2b FV urine</td>
<td>Medium conversion (50%) to self-sampling</td>
<td>72.0</td>
<td>130,324,361</td>
<td>2,731,060</td>
<td>47.72</td>
<td>91,144</td>
<td>1,425</td>
<td>9.09</td>
</tr>
<tr>
<td>2c FV urine</td>
<td>High conversion (75%) to self-sampling‡</td>
<td>72.0</td>
<td>117,657,464</td>
<td>2,726,597</td>
<td>43.15</td>
<td>88,761</td>
<td>1,326</td>
<td>13.66</td>
</tr>
<tr>
<td>2d Vaginal</td>
<td>Low conversion (25%) to self-sampling</td>
<td>72.0</td>
<td>144,216,324</td>
<td>2,735,524</td>
<td>52.72</td>
<td>94,123</td>
<td>1,532</td>
<td>4.09</td>
</tr>
<tr>
<td>2e Vaginal</td>
<td>Medium conversion (50%) to self-sampling</td>
<td>72.0</td>
<td>132,774,492</td>
<td>2,731,060</td>
<td>48.62</td>
<td>91,144</td>
<td>1,452</td>
<td>8.19</td>
</tr>
<tr>
<td>Scenario 3: self-sampling only offered to those who do not currently screen (non-attenders)</td>
<td>3a FV urine</td>
<td>Low uptake of self-sampling (8%)</td>
<td>74.2</td>
<td>158,924,528</td>
<td>2,824,676</td>
<td>56.26</td>
<td>99,482</td>
<td>1,598</td>
</tr>
<tr>
<td>3b FV urine</td>
<td>Medium uptake of self-sampling (15%)</td>
<td>76.2</td>
<td>161,782,605</td>
<td>2,898,778</td>
<td>55.81</td>
<td>101,825</td>
<td>1,589</td>
<td>1.00</td>
</tr>
<tr>
<td>3c FV urine</td>
<td>High uptake of self-sampling (20%)</td>
<td>77.6</td>
<td>163,824,088</td>
<td>2,951,709</td>
<td>55.50</td>
<td>103,499</td>
<td>1,583</td>
<td>1.31</td>
</tr>
<tr>
<td>3d FV urine</td>
<td>High uptake of self-sampling (20%) plus 10% additional uptake of routine screening</td>
<td>80.4</td>
<td>169,877,461</td>
<td>3,058,264</td>
<td>55.55</td>
<td>107,263</td>
<td>1,584</td>
<td>1.26</td>
</tr>
<tr>
<td>3e Vaginal</td>
<td>Low uptake of self-sampling (8%)</td>
<td>74.2</td>
<td>159,076,981</td>
<td>2,824,676</td>
<td>56.32</td>
<td>99,482</td>
<td>1,599</td>
<td>0.49</td>
</tr>
<tr>
<td>3f Vaginal</td>
<td>Medium uptake of self-sampling (15%)</td>
<td>76.2</td>
<td>162,068,454</td>
<td>2,898,778</td>
<td>55.91</td>
<td>101,825</td>
<td>1,592</td>
<td>0.90</td>
</tr>
<tr>
<td>3g Vaginal</td>
<td>High uptake of self-sampling (20%)</td>
<td>77.6</td>
<td>164,205,220</td>
<td>2,951,709</td>
<td>55.63</td>
<td>103,499</td>
<td>1,587</td>
<td>1.18</td>
</tr>
<tr>
<td>3h Vaginal</td>
<td>High uptake of self-sampling (20%) plus 10% additional uptake of routine screening</td>
<td>80.4</td>
<td>170,258,592</td>
<td>3,058,264</td>
<td>55.67</td>
<td>107,263</td>
<td>1,587</td>
<td>1.14</td>
</tr>
<tr>
<td>Scenario 4: self-sampling offered as an option to all—resulting in 15% (medium) uptake in self-sampling in non-attenders</td>
<td>4a FV urine</td>
<td>Low conversion (25%) to self-sampling in those who currently screen</td>
<td>76.2</td>
<td>149,115,708</td>
<td>2,894,315</td>
<td>51.52</td>
<td>99,144</td>
<td>1,504</td>
</tr>
<tr>
<td>4b FV urine</td>
<td>Medium conversion (50%) to self-sampling in those who currently screen</td>
<td>76.2</td>
<td>136,448,811</td>
<td>2,889,852</td>
<td>47.22</td>
<td>96,463</td>
<td>1,415</td>
<td>9.59</td>
</tr>
<tr>
<td>4c FV urine</td>
<td>High conversion (75%) to self-sampling in those who currently screen‡</td>
<td>76.2</td>
<td>123,781,914</td>
<td>2,885,388</td>
<td>42.90</td>
<td>93,783</td>
<td>1,320</td>
<td>13.91</td>
</tr>
<tr>
<td>4d Vaginal</td>
<td>Low conversion (25%) to self-sampling in those who currently screen</td>
<td>76.2</td>
<td>150,626,622</td>
<td>2,894,315</td>
<td>52.04</td>
<td>99,144</td>
<td>1,519</td>
<td>4.77</td>
</tr>
</tbody>
</table>

Continued
FV urine sampling and £36.17 for vaginal self-sampling (online supplemental table 16).

A higher HPV prevalence might be expected in some non-attenders. The cost per complete screen for the FV urine self-sampling (£42.74) and vaginal self-sampling (£44.59) was less than the cost for SoC (£60.99) even when the high HPV positivity values (used in the DSA) were used in years 1, 2 and 3.

**DISCUSSION**

**Main findings**

The results of the base case model indicate that self-sampling for cervical cancer screening costs less than clinician-collected sampling assuming equivalent performance of HPV testing on self-collected and clinician-collected samples. The magnitude of savings to a screening programme is dependent on whether self-sampling is offered to non-attenders or to everyone eligible for screening, and the impact on uptake. With a steady increase in the HPV-vaccinated cohort entering the NHSCSP, the prevalence of HPV will fall over time and would further reduce screening costs, particularly in self-sampling pathways where a negative HR-HPV result does not require an appointment.

The self-sampling pathway currently requires an additional step for clinician-collected sampling following a positive HPV result, which might be avoided with newer technologies such as DNA methylation. This additional step means that the overall uptake must be higher to result in the same number of complete screens as SoC due to LTFU.

In some of the scenarios assessed, the NHSCSP would make considerable savings while increasing the number of complete screens (table 3). If self-sampling were only offered to existing non-responders and there was low uptake (scenario 3a), it would result in more colposcopies (and therefore more CIN2+ diagnoses) than SoC, at a reduced cost per screen (£0.55 saving compared with SoC). However, even if self-sampling was targeted to non-screeners, some regular screeners may swap to self-sampling, as observed in the Netherlands. Therefore, a 25% conversion to self-sampling with 15% uptake in non-responders (scenario 4a) may be a more reasonable scenario to consider. In this case, there would also be additional colposcopies (n=2340) at a reduced cost per screen compared with SoC. However, if there was 50% conversion to self-screening or higher (and 15% uptake in non-responders) (scenario 4b), although the cost per screen would be considerably lower than for SoC, there would be fewer colposcopies overall. It would be difficult to predict the uptake and switching rate if self-sampling were offered; it is likely to differ between settings and be strongly influenced by the messaging around self-sampling.

**Strengths and limitations**

This is the first study to model the costs of vaginal swab and FV urine self-sampling within the NHSCSP. As such, it provides valuable data to inform decision-making about the future use of self-sampling in England, elsewhere in the UK and other countries with similar screening programmes.

As with all models, several assumptions were made for simplicity or due to the sparsity of data available to inform the parameters. One crucial assumption is that HPV testing of self-collected samples has (or will have) equivalent performance to clinician-collected samples. This assumption was made based on previous evaluations indicating non-inferiority of sensitivity for CIN2+ on self-collected samples when using PCR-based assays. Further optimisation of HPV assays for self-collected samples is anticipated if self-sampling was incorporated into screening programmes. There are a number of ongoing trials that will provide real-world data supporting this assumption. If the relative specificity for HPV were inferior for self-collected samples, this would increase the cost per screen by a small amount for the self-sampling strategies as it would result in additional sample collection and cytology costs in the small number of false positives. However, in most cases, cytology triage would then rule out the need for colposcopy so it
would not add unnecessary colposcopy-related costs. If the sensitivity for CIN2+ detection were inferior for self-collected samples, more cases would be missed than in SoC and therefore it would be most appropriate to offer self-sampling to non-attenders who would otherwise not screen.

In a high uptake setting such as England, there is a risk in changing well-established screening programmes, since shifting to self-sampling could result in a temporary or long-term drop in uptake. It is not sufficient for HPV tests to demonstrate high performance; to encourage uptake and confidence in the screening programme, it is crucial that people offered screening are informed about and have confidence that testing is highly accurate. It will be important to collect real-world evidence, provide education/ awareness programmes for women and clinicians and evaluate changes carefully to ensure that overall uptake is maintained or improved to further improve the detection and treatment of cervical cancer and CIN. In the context of increasingly vaccinated cohorts entering the NHSCSP with lower HPV prevalence, the cost and cost-effectiveness of the programme will decrease and therefore solutions such as self-sampling (and potentially DNA methylation triage on the same sample in place of cytology) will be of great interest to programme managers and decision-makers as they can reduce the costs of the programme and the burden on healthcare services.

Where costs for England were calculated (in scenario analyses), it was assumed that HPV positivity was the same in attenders and non-attenders. This is unlikely to be the case; studies indicate a higher prevalence of CIN2+ and cervical cancer in long-term non-screening groups compared with populations who regularly screen. However, the results of the DSA (figure 2) and scenario analysis indicate that self-sampling would cost less than clinician-collected sampling, even in a population with higher HPV positivity. In our base case model, fewer people received colposcopy in the self-sampling strategies due to the additional LT FU at the point where HPV-positive people must attend to provide a sample for cytology. There were limited data on the probability of returning self-samples and attendance for cervical sampling following an HPV positive result, both of which will be informed by future population-based evaluations and may change over time if self-sampling were widely promoted and became ‘the norm’. Variations in these probabilities impact the cost per screen but self-sampling remains the cheaper option even when these probabilities were low (figure 2). Future developments enabling molecular triage of self-collected samples for colposcopy referral would simplify the pathway and eliminate this risk of LTFU. Its impact on cost per screen is unclear as it would largely depend on the cost of molecular triage, which is not currently approved for use within the NHSCSP.

The focus of the model was on the short-term costs related to screening. The number and cost per CIN2+/cancer diagnosis were not calculated, and the future savings and health benefits associated with avoiding progression to cancer or earlier detection of cancer were not considered; this would require a model with a longer time horizon. If the same number of women with the same CIN2+ prevalence were screened in each strategy, then there would be fewer CIN2+ diagnoses in the self-screening strategies due to the additional LTFU, reducing the number of colposcopies (unless molecular triage avoided the need for cytology). However, in practice, if multiple ways of screening were offered, we would anticipate the uptake and CIN2+ prevalence to differ between the sampling groups which would then impact the overall number of CIN2+ diagnoses and the cost per CIN2+ diagnosis.

Interpretation

Previous cost evaluations of self-sampling for HPV testing support our finding that self-sampling costs less than routine cervical screening.27 As a strategy to offer to non-attenders who decline routine screening, self-sampling may increase national screening coverage closer to the target of 80%, reversing the downward trend in screening uptake seen over the past decade and during the COVID-19 pandemic. Introduced as a choice for all, self-sampling has the potential to save money and increase coverage.

It was assumed that high-throughput testing platforms would be used for HPV testing of urine samples. If self-collected samples require even a few more minutes of laboratory staff time per sample, this would increase the cost per HPV test and may be impractical when scaled up to 2500 samples a day, the current throughput at one of the NHSCSP laboratories (personal communication). Therefore, full rollout to everyone eligible for screening is dependent on laboratory procedures being automated for testing self-collected samples.

There may be hesitancy in introducing a change to screening for the whole eligible screening population. A 2017 Dutch study assessing the switch from cytology to primary HR-HPV screening with the simultaneous introduction of vaginal self-sampling as an option offered to all observed a decrease in participation (from 64% to 61%). Other recent changes to the delivery of healthcare and the widespread use of self-testing in the context of the COVID-19 pandemic may play a role in increasing the acceptability of self-sampling. Furthermore, there is evidence that urine self-sampling is more acceptable than vaginal self-sampling due to it being less invasive and easier to collect and women feeling more confident providing a urine sample compared with a vaginal sample. As such, self-sampling using urine may align with patient preferences, address screening inequalities and remove some barriers to clinician-collected cervical and/or vaginal self-sampling.
Future research
Our model represents one pathway for self-screening. There are alternative pathways, self-sampling devices and ways to distribute self-sampling kits, some of which have been assessed in trials. For example, self-sampling could be offered to non-attenders after an initial offer of routine screening is ignored, either by sending another invite or the self-collection kit. Our model used an opt-in strategy for the initial screen and an opt-out approach for the 12-month recall. One alternative is an opt-out strategy for the initial invite (i.e., sending the self-sample kit with the invite), a strategy successfully used in the UK for bowel cancer screening. Opt-out strategies have the advantage of increasing uptake but increase the initial costs due to the wastage of unused kits. Alternatively to a letter invitation may also be modelled, for example, offering self-sampling within primary care or community settings. An Australian study found high uptake (86%) in women who were offered vaginal self-sampling for HPV screening while attending a GP appointment. Uptake was 68% (of which 66% returned the sample) in a study conducted in England where women could either collect the self-sample while at the clinic or after returning home. Real-world evaluations to assess the best way to offer screening would provide invaluable insight, particularly if mixed methods were used to understand the reasons for any change in uptake. An evaluation of whether an HPV test on the second sample taken for cytology is of benefit would also inform this part of the screening pathway if self-sampling were adopted.

In our model, for each sampling strategy, the same type of sampling was used for routine and recall screening. Alternatively, clinician-collected sampling could be used (for all strategies) in years 2 and 3, since HPV prevalence is considerably higher in the recall group. The increase in recent and ongoing research activities around urine self-sampling for HPV testing indicates that there is a lot of interest in its potential as an alternative method of cervical screening. To further inform screening programmes, further research is needed to optimise urine collection, the volume of urine collected, transport media, and compatibility of new or existing HPV assays. The screening programme will need to evolve as the cohort changes with increasing numbers vaccinated against HPV and a reduction of HPV infection, pre-cancerous lesions and cervical cancer.

Conclusion
Cost is not a barrier to the use of self-sampling within the NHSCSP. Self-sampling for primary HPV testing provides a less costly alternative to routine clinician-collected cervical screening with the additional benefit of improving user experience and choice.

Many countries are considering how best to implement self-sampling options for HPV primary testing. This study directly compares two self-sampling methods to provide evidence on the scale of cost-savings which could be realised.

REFERENCES
1 World Health Organization. WHO guideline for screening and treatment of cervical pre-cancer lesions for cervical cancer prevention. 6 July 2021 Available: https://www.who.int/publications/i/item/9789240030824

Contributors SH, KPS and VS designed the study and model structure with support and input from KT and EJC. KPS built the main model and ran the analyses, VS developed the scenarios analysed with input from SH, KPS, VS and SH identified data to inform the model parameters and transformed these where necessary. SH helped inform model parameters. EJC led on patient and public engagement, SH, KPS, VS, KT and EJC contributed to data interpretation. The paper was drafted by SH, KPS, VS and EJC with input from AS, KT and EJA. The project was overseen by SH, with input from KT and EJA. SH is the guarantor of this study.

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Disclaimer
The design, results and interpretation of the study were generated independently by the authors. Novosanis was given the opportunity to review the manuscript for medical and scientific accuracy.

Competing interests
SH, KPS, VS, KT and EJA are employed by Aquarius Population Health, which received funding for this study. Aquarius Population Health works on projects related to diagnostics for commercial and academic clients and as part of grant-funded projects. EJC is a National Institute for Health Research (NIHR) Advanced Fellow (NIHR300650), and her work is funded by the NIHR Manchester Biomedical Research Centre (I-S-BRC-1215-20007). AS is a clinical scientist employed by the NHS working within the NHSCSP in the capacity of HPV lead scientist and pathway manager.

Patient and public involvement
Patients and/or the public were involved in the design, conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication
Not required.

Ethics approval
No ethical approval was required or sought as only secondary data sources were used; there was no randomisation or change to patient care, and no patient-identifying information was obtained or used.

Provenance and peer review
Not commissioned; externally peer reviewed.

Data availability statement
All data relevant to the study are included in the article or uploaded as supplemental information. The model is not publicly available.

Supplemental material
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