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1	Cancer Prevention Group
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3	Faculty of Life Sciences & Medicine
4	King's College London
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8	16/18 GENOTYPING IN TRIAGE OF PERSISTENT
9	HUMAN PAPILLOMAVIRUS INFECTIONS WITH NEGATIVE
10	CYTOLOGY IN THE ENGLISH CERVICAL SCREENING PILOT
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12	Running title: HPV 16/18 triage for persistent infections
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51 **KEYWORDS**

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53 Cervical cancer, screening, triage, high-risk human papillomavirus,	genotyping
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56 ABSTRACT

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Background. In the English pilot of primary cervical screening with high-risk human 58 papillomavirus (HR-HPV), we exploited natural viral clearance over 24 months to minimise 59 60 unnecessary referral of HR-HPV+ women with negative cytology. Three laboratories were 61 permitted to use 16/18 genotyping to select women for referral at 12-month recall. We estimated the 62 clinical impact of this early genotyping referral. 63 Methods. The observed numbers of women referred to colposcopy and with detected high-grade 64 cervical intraepithelial neoplasia (CIN2+), and of women who did not attend early recall in the three 65 laboratories were compared with those estimated to represent a situation without an early 66 genotyping referral. The 95% confidence intervals (CI) for the differences between the protocols 67 68 were calculated by using a parametric bootstrap. 69 70 Results. Amongst 127,238 screened women, 16,097 (13%) had HR-HPV infections. The 71 genotyping protocol required 5.9% (95% CI: 4.4-7.7) additional colposcopies and led to a detection 72 of 1.2% additional CIN2+ (95% CI: 0.6-2.0), while 2.3% (95% CI: 2.1-2.5) fewer HR-73 HPV+/cytology- women did not attend the early recall compared with the non-genotyping 74 protocol. 75 **Conclusions.** In a screening programme with high quality of triage cytology and high adherence to 76 77 early recall, 16/18 genotyping of persistent HPV infections does not substantially increase CIN2+ 78 detection. 79 80

81 BACKGROUND

82

In England, the National Health Service (NHS) has provided cervical screening since 1988 through 83 84 a "call and recall" Cervical Screening Programme (CSP). Women become eligible for screening at 85 age 25 years. Thereafter, they are recalled for cytological screening every three years until age 50 86 years, and then five yearly until the age of 64 years. Nationwide roll-out of primary high-risk 87 human papillomavirus (HR-HPV) screening triaged with cytology is planned to be implemented by 88 the end of 2019. In 2013, a pilot of primary cervical screening with HR-HPV testing was set up in six large CSP laboratories, accounting for about 13% of the nationally screened population.¹ 89 90 91 The aim of substituting cytology with HR-HPV testing is to achieve greater sensitivity and increase 92 screening intervals. Because of relatively poor specificity, however, reflex cytology is required to identify those HR-HPV+ women who require colposcopy referral. In several countries including the 93 USA and Australia, HPV 16/18 genotyping is being used at baseline to identify women with 94

95 negative cytology at increased risk of underlying cervical intraepithelial neoplasia (CIN), for
96 immediate referral.^{2, 3} In these cases, the decision to refer HPV 16/18 positive women is made on a
97 single screening sample.

98

99 The English pilot also recognised a potential value of HR-HPV genotyping in triage, but it was 100 considered that implementing it in the same way as those other countries, i.e. based on a single sample, would lead to an unsustainable increase in the demand for colposcopy. Hence, women with 101 102 HR-HPV infections have been managed as shown in Table 1. At baseline and at 12-month early recall, the selection of HR-HPV positive women for colposcopy relied on positive cytology, defined 103 104 as borderline change in squamous or endocervical cells or worse. This is equivalent to atypical 105 squamous cells of undetermined significance (ASCUS, and atypical glandular cells of undetermined 106 significance, AGUS, in the Bethesda 2014 classification), or worse. Evidence of 24-month

persistence of a HR-HPV infection, regardless of concurrent cytology, also triggered referral for
colposcopy. Additionally, three of the six laboratories used HPV 16/18 genotyping as a basis for
more rapid referral for colposcopy in cases where there was persistent infection at the 12-month
early recall in the absence of cytological abnormality. This means that a decision to refer cytologynegative women to colposcopy based on 16/18 genotyping is made only after two consecutive HRHPV positive samples.

113

114 Both of these triage protocols were aimed at reducing the need for colposcopy by exploiting the substantial natural clearance rates of all HR-HPV infections, including HPV 16/18.4-6 The non-115 116 genotyping protocol with two early recalls within 24 months after screening, aimed to maximise the 117 reduction in the need for colposcopy but was potentially vulnerable to the risk of non-adherence with an additional early recall. The genotyping protocol, expediting a referral of women with the 118 most high-risk infections and reserving the second early recall for those whose infections are less 119 120 likely to progress to cancer, aimed to reduce loss to follow-up at the second early recall and to 121 maximise the detection of CIN2+ lesions requiring treatment. Hence, we evaluated the differences 122 between the two protocols in the overall frequency of referral for colposcopy, detection of CIN2+ 123 and CIN3+, and the loss to follow-up at early recall.

124

- 125 MATERIALS AND METHODS
- 126
- 127 The pilot

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129 The pilot started in May 2013 and the main outcomes have been described previously in detail.⁷

130 Briefly, six English CSP laboratories converted around a third of their screening population from

- 131 primary liquid-based cytology (LBC) to primary HR-HPV screening. Conversion was population-
- 132 based. The selection of administrative areas for conversion was not determined in a random process.

133 Rather, the laboratories considered practical issues such as maintaining a single clinical

134 management protocol in colposcopy practices serving each administrative area. During the pilot, the

135 population age range and recommended screening intervals remained unchanged.

136

137 Screening and diagnostic tests

138

139 Screening samples were taken within primary care and were collected in either SurePath (Becton 140 Dickinson, Sparks, MD) or ThinPrep (Hologic, Marlborough, MA) LBC media. SurePath was used 141 in three laboratories, while ThinPrep was used in the other three. In 2013-2014, two laboratories 142 used Cobas 4800 (Roche, Rotkreuz, Switzerland, or Branchburg, NJ); two used RealTime (Abbott, Wiesbaden, Germany); and the remaining two used APTIMA (Hologic, Manchester, UK). Cobas 143 144 and RealTime are HR-HPV DNA genotyping assays that report HPV 16 and HPV 18 separately 145 from the 12 other HR-HPV genotypes, which are reported in combination. APTIMA is an HR-HPV 146 mRNA assay detecting the 14 HR-HPV genotypes in combination.

147

All HR-HPV assays had previously been approved for primary screening within the CSP. Triage
cytology was read under routine conditions with knowledge of a HR-HPV infection, and was
quality controlled to CSP standards. Colposcopy was conducted according to national clinical
practice guidelines. All diagnoses reflect routine cytopathology and histopathology in the CSP.

152

153 Study design

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The present study was designed to compare the outcomes of screening in the pilot with and without HPV 16/18 triage at the 12-month early recall. As the first screening invitation is sent at age 24.5 years, we included women aged 24-64 years at the time of the screening test. Additionally, women were included if they had been screened during the first (prevalence) round of primary screening with HR-HPV testing from the beginning of the pilot in May 2013 until December 2014 in the three
Cobas or RealTime laboratories that used the HR-HPV genotyping information for the management
of HR-HPV positive women (Table 1). Data on all subsequent tests and diagnoses were retrieved
from the laboratories' information systems until May 2017, which gave all women 29-49 months of
follow-up after the primary screening test.

164

165 Women screened in the three laboratories that did not use HR-HPV genotyping information for the 166 management of HR-HPV positive women were not included as a comparator in this post-hoc analysis. Two of these laboratories used the APTIMA assay. Unlike DNA assays that typically 167 168 detect both transient infections and those integrated into a host's genome, APTIMA has been 169 designed to detect (predominantly) the latter type of infections. It has indeed been observed that this assay typically detects fewer HR-HPV infections than DNA assays, which ultimately leads to lower 170 colposcopy rates in a routine screening programme.^{8,9} Consequently, using APTIMA data as a 171 comparator would have introduced the effect of the assay's different molecular target into the 172 173 comparison of the triage protocols and hence could substantially affect analysis, particularly in 174 terms of the number of colposcopies.

175

The prevalence screening episode for each woman was defined as starting with the first test recorded during the pilot period, i.e. the primary (baseline) test, and closed with any early recall tests or colposcopies. If the first recorded pilot test was preceded by another test within the two prior years, or if the test's management code identified it as a follow-up to a recent cervical abnormality, the episode was excluded from further analysis. This is because those tests were unlikely to have been taken for the purpose of primary screening. Tests were linked using each women's unique English NHS numbers.

183

In this analysis, the infecting HR-HPV genotype was determined at the primary test and remained fixed even if the genotype changed by the 12-month early recall. The effect of a genotype change on the studied outcomes was addressed in a sensitivity analysis (see below). Women were included in the 16/18 category regardless of any co-infecting genotypes.

188

Our primary endpoints were (1) the total number of colposcopies performed, (2) the number of HR-HPV positive/cytology negative women not adhering to early recall, and (3) the number of detected CIN2+ lesions for each triage protocol. CIN2+ was chosen as one of the primary endpoints as this is the threshold for treatment, but the results are also presented for the more reproducible endpoint of CIN3+.¹⁰

194

195 These outcomes were estimated based on aggregated observed data from the three genotyping 196 laboratories (Table 2), and the following two sets of assumptions. Firstly, we assumed that all 197 women would be referred as expected on the basis of their screening outcomes (Table 1). For a 198 minority of women in the data where this did not happen (gray cells in Table 2), we assumed that 199 they would have the same clinical outcomes as women who were referred as expected. As this was 200 done consistently for both protocols, the calculated total numbers of colposcopies, CIN, and women 201 not returning for early recall under the genotyping protocol differ slightly from those that were 202 directly observed. Secondly, the 24-month outcomes in cytology-negative women persistently 203 infected with HPV 16/18 at 12 months could not be directly observed for the non-genotyping protocol. We estimated them on the following assumptions: a) that attendance at 24-month early 204 205 recall and colposcopy would be the same as that observed among women infected with other HR-206 HPV genotypes, b) that persistence of HR-HPV infections between the 12- and 24-month early 207 recalls would be as that observed in a fourth pilot laboratory, which reported HR-HPV genotyping 208 data but implemented a non-genotyping triage protocol (Table 1), and c) that CIN2+ and CIN3+

prevalent at 12-month early recall would still be detectable at 24-month early recall, i.e. that there
was no excess regression or progression between the two early recalls.¹¹

211

212 Two sensitivity analyses were undertaken to assess the robustness of the findings. In the first of 213 these, we addressed a subgroup of women with HPV 16/18 infections and persistently negative 214 cytology at 12 months. Among these women, a relatively large proportion did not have a record of 215 referral for colposcopy (Table 2). In the base case analysis, we assumed that this was at random. In 216 the sensitivity analysis, we used two conventional extreme assumptions for parameters with uncertain true values, i.e. that (analysis S1a) all women in this subgroup would have attended 217 218 colposcopy with CIN2+ detection doubled from the (observed) base case value; or (analysis S1b) 219 only half of the women in this subgroup would attend with CIN2+ detection halved from the base 220 case value. A lower CIN2+ detection could be expected, for example, in cases where HPV 16/18 221 infection had cleared by the 12-month early recall, but the woman remains HR-HPV positive. Indeed, this situation represented about two-thirds of the women without a record of referral to 222 223 colposcopy at 12 months in the observed data. In the second sensitivity analysis, persistence of 224 infections between the 12- and 24-month early recalls in women with negative cytology and HPV 16/18 infections (which played a role in estimating the number of colposcopies in the non-225 226 genotyping protocol) was based on a small dataset from a single laboratory (N=98). We varied the 227 proportion of women with persistent infections as: (analysis S2a) the lower 5% confidence limit; or 228 (analysis S2b) the upper 95% confidence limit.

229

230 Statistical analysis methods

231

For both the number of colposcopies and the number of CIN2+ lesions detected, the relative difference was reported as the ratio between the absolute difference in the totals for the genotyping and the non-genotyping protocols (numerator) and the total number in the non-genotyping protocol

(denominator). For the number of women not adhering to early recall, the total number with HRHPV positive cytology negative samples at baseline was used as the denominator. The positive
predictive value (PPV) of colposcopy for CIN2+ and CIN3+ was calculated using the number of
women attending colposcopy as the denominator. Detailed formulae are reported in Supplementary
information.

240

We obtained 95% confidence intervals (CI) for detection of CIN2+, number of colposcopies and
loss of adherence to follow-up at the 12- and 24-month early recall using a parametric bootstrap.
More precisely, following the flows in Figure 1, we sampled the numbers in each category based on
the observed data in Table 2; this process was repeated 10,000 times and the empirical distributions
of the resulting numbers of colposcopies, CIN2+ and CIN3+, and women not attending early recall
were used to form a 95% CI. The statistical software R (version 3.4.1) was used for all analysis.¹²

247

248 **RESULTS**

249

250 Observed screening outcomes by HR-HPV genotype

251

252 In total, 127,238 women were screened in the three genotyping laboratories in 2013-2014. Of these, 16,097 (13%) had a positive HR-HPV test result, 5287 (4%) with positive and 10,810 (8%) with 253 negative cytology (Table 2). In total, 8759 (7%) HR-HPV positive women underwent a colposcopy, 254 leading to detection of 2859 (2%) CIN2+ and 1763 (1%) CIN3+ (Table 3 and Figure 1). These 255 256 numbers include detection following the recommended management protocol, including early recall 257 as well as any colposcopies undertaken outside the protocol. Colposcopies and CIN observed 258 outside of the recommended protocol, for example those after an immediate referral of HR-HPV 259 positive cytology negative women at baseline, were infrequent and were not included in further

analyses. They amounted to 310 (4%) colposcopies, 31 (1%) CIN2+, and 16 (1%) CIN3+ (Figure
1).

262

263 Detection of CIN2+ was highest amongst women screened at age 24-29 years: 6.6% and 4.1% for 264 CIN2+ and CIN3+, respectively. By comparison, the numbers were 1.6% and 1.0% at 30-49, and 265 0.5% and 0.3% at 50-64 years of age. A case of CIN2+ was detected for every three colposcopies at 266 age 24-29 years and for every six colposcopies at age 50-64 years. For CIN3+, the numbers of 267 colposcopies needed at these ages were four and 10 per case, respectively (data not tabulated). 268 269 Half of all CIN2+ (50%, 1423/2859) and 55% (968/1763) of CIN3+ were diagnosed in women 270 infected with HPV 16, whereas 9% (247/2859 and 153/1763) of CIN2+ and CIN3+ were detected in women with HPV 18 without HPV 16 (Table 3). Other genotypes without either HPV 16 or 18 271 272 were detected in 41% (1189/2859) of CIN2+ and 36% (642/1763) of CIN3+. Amongst all 4047 273 women infected with HPV 16, 35% (1423/4047) were ultimately diagnosed with CIN2+ and 24% 274 (968/4047) with CIN3+. For the 1160 women infected with HPV 18, this was 21% (247/1160) and 275 13% (153/1160), respectively, and for the remaining 10,890 women with other HR-HPV infections 276 it was 11% (1189/10,890) and 6% (642/10,890), respectively (Table 3).

277

278 During the same period, the fourth laboratory with HR-HPV DNA genotyping information, but 279 implementing a non-genotyping triage protocol, screened 15,831 women with HR-HPV testing. Of these, 1714 (11%) had a positive HR-HPV test result, 1274 (8%) with negative and 440 (3%) with 280 281 positive cytology. This was similar to the screening results in the three substantially larger 282 laboratories included in the main analysis. Among the 98 women with HPV 16/18 infections and 283 negative cytology persisting at 12 months, the infection persisted until 24 months in 73 (74%). This 284 proportion was virtually constant across age groups (data not tabulated). Among women with HPV 285 16/18 infections who attended colposcopy after the 24-month early recall, the observed PPV for

- CIN2+ was 27% (19/71), with 15% (8/54) if they had negative cytology, and 65% (11/17) if they
 had positive cytology.
- 288

289 Estimating the impact of the genotyping triage protocol

291	The genotyping protocol generated detection of 2869 CIN2+ and 1769 CIN3+ resulting from 8750
292	colposcopies among the 127,238 screened women (Table 4). More than 90% of all CIN2+ (91%,
293	2614/2869) were detected after a referral with positive cytology at either the baseline test or at the
294	12-month early recall. An additional 5% (133/2869) of CIN2+ were detected after a referral of HPV
295	16/18 positive women with persistently negative cytology at 12 months, and the final 4%
296	(123/2869) of CIN2+ were diagnosed at 24-month early recall amongst women persistently infected
297	with other HR-HPV genotypes. This pattern was very similar for the detection of CIN3+.
298	
299	An estimated 1741 cytology negative women with a positive baseline HR-HPV test result did not
300	attend the 12-month early recall. Additionally, 637 women who attended the 12-month early recall
301	did not attend a recommended 24-month early recall. In total, we estimate that 22% (2378/10,810)
302	of HR-HPV positive cytology negative women did not attend or complete early recall.
303	
304	Estimating the impact of the non-genotyping triage protocol
305	
306	With this protocol, a total of 2835 CIN2+ and 1751 CIN3+ would be detected as a result of 8260
307	colposcopies among the 127,238 screened women (Table 4). Again, >90% of all high-grade CIN
308	would be detected following positive triage cytology at baseline or at 12-month early recall. The

- remaining CIN2+ would be detected at the 24-month early recall for persistent HR-HPV.
- 310

311	Referring all persistently HR-HPV positive women with negative cytology at 12 months to an
312	additional 24-month early recall would result in 8% (864/10,810) of women not attending, in
313	addition to the 16% (1741/10,810) not attending the 12-month early recall. In total, we estimate that
314	24% (2626/10,810) of HR-HPV positive cytology negative women would not have completed the
315	recall under the non-genotyping triage protocol.
316	
317	PPV of a referral for colposcopy
318	
319	The PPVs for CIN2+ were high when a colposcopy was undertaken following a positive cytology
320	triage test result: 41% (2135/5163) at baseline and 35% (479/1369) after the 12-month early recall
321	(Table 4).
322	
323	In women infected with non-16/18 HR-HPV genotypes referred after the 24-month early recall, the
324	PPV of a colposcopy was 10% (123/1198; Table 4). At this point, positive cytology was not used as
325	a condition for a colposcopy. Nevertheless, the laboratories did report the cytology grade and the
326	PPV for CIN2+ remained high, 29% (66/228), amongst women with cytological abnormalities, and
327	much lower, 6% (51/907), amongst women who remained cytologically negative (data not
328	tabulated; cytology of the remaining 9 out of 1144 women with a colposcopy (Table 2) was not
329	graded).
330	
331	In women with HPV 16/18 positive persistently negative cytology, the PPV for CIN2+ was 13%
332	(133/1020) at the 12-month early recall. At 24 months, the PPV for persistent HPV 16/18
333	infections, regardless of cytology, is estimated at 18% ((221-123)/(1728-1198), Table 4). The PPV
334	could not be reliably estimated separately by cytology but as reported earlier, it was 15% among 54
335	cytology negative women in the fourth genotyping laboratory.
336	

In all cases, the PPVs for CIN3+ were approximately half those for CIN2+.

338

339 Comparison of the two protocols

340

341	We estimate that the genotyping protocol would detect an additional 34 (95% CI: 26-43) CIN2+
342	and 18 (95% CI: 13-24) CIN3+ cases among the 127,238 screened women, representing 1.2% (95%
343	CI: 0.9-1.5) of CIN2+ and 1.0% (95% CI: 0.8-1.4) of CIN3+ cases detectable by the non-
344	genotyping protocol (Table 5). It would result in 5.9% (95% CI: 5.0-6.9) more colposcopies; 8750
345	(95% CI: 8572-8924) vs. 8260 (95% CI: 8079-8444), a difference of 490 (95% CI: 420-562). It
346	would also result in 2.3% (95% CI: 2.1 to 2.5) fewer HR-HPV positive cytology normal women not
347	completing their recommended early recall; 2378 (95% CI: 2283-2475) vs. 2626 (95% CI: 2520-
348	2731), a difference of 248 (95% CI: 226-270). The differences between the two protocols were very
349	similar across all age groups (Table 5).
350	

351 The outcomes were not materially affected by varying the assumptions on the attendance at colposcopy and prevalence of CIN2+ in HPV 16/18 positive women with persistently negative 352 353 cytology. Under the favourable scenario for the genotyping protocol (analysis S1a: a high 354 attendance at colposcopy and a high PPV), the latter would increase the need for colposcopy by 355 6.1% (95% CI: 5.2-7.0) and CIN2+ detection by 1.6% (95% CI: 1.3-1.9). Under the unfavourable scenario (analysis S1b: a low attendance at colposcopy and a low PPV), the estimates would be 356 lower at 4.7% (95% CI: 3.8-5.6) and 0.3% (95% CI: 0.1-0.6), respectively. Varying the proportion 357 of women infected with HPV 16/18 who remain HR-HPV positive by 24 months produced a range 358 359 in the extra demand for colposcopy between 6.6% (analysis S2a, 95% CI: 5.6-7.6) and 5.3% 360 (analysis S2b, 95% CI: 4.5-6.1).

361

363 **DISCUSSION**

364

Using data from the English HPV pilot we estimated there would be a small increase in CIN2+ 365 366 detection for HPV 16/18 genotyping compared with non-genotyping triage protocols for women with persistent HR-HPV infections and negative cytology. However, more rapid referral of 367 368 persistently HPV 16/18 positive women with negative cytology would increase the number of 369 colposcopies by 6%, which appears to be disproportionate with respect to an estimated increase in 370 detected CIN2+ of 1%. This is a consequence of both reasonably high compliance with repeated 371 testing in early recall observed in the pilot (close to 80%), and highly sensitive stratification of risk 372 by cytology triage. The latter identified 75% of all CIN2+ at baseline and an additional 17% at 12-373 month early recall, with a high PPV on both occasions of over 30%. A very small pool of CIN2+ remained to be identified solely by HR-HPV genotyping but the PPV was substantially lower at 374 around 10%. 375

376

As HPV 16/18 lesions are more likely to progress to cancer,¹³⁻¹⁵ our finding of a 1% higher 377 detection of CIN2+ and CIN3+ with a faster referral of HPV 16/18 positive women warrants 378 379 consideration. This relatively small additional increase in the number of detected CIN2+ achieved 380 by genotyping persistent HR-HPV infections would be observed on top of the approximately 50% increase achieved in the pilot by substituting cytology with HR-HPV testing,⁷ and most of these 381 cases would be detected in women below 30 years of age, when the likelihood of regression of 382 CIN2+ is highest.¹⁶ Persistently negative cytology is often associated with early infections and 383 lesions detectable only through HR-HPV testing have been hypothesised to be small.¹⁷ Given the 384 long duration of progression of CIN lesions to cervical cancer, ^{16, 18, 19} a delay of 12 months in 385 diagnosing these cytologically negative lesions is unlikely to be associated with a significant risk of 386 387 interval cancer, provided women adhere to early recall.

388

389 HPV 16/18 genotyping has been recommended for an immediate referral of HR-HPV positive/cytologically negative women in countries such as the USA^{2, 20} and Australia.³ In Europe, 390 the attitude towards using genotyping in this manner has so far been more conservative,²¹⁻²³ and 391 392 baseline referral was not tested in the English pilot out of concern that it would lead to an 393 unsustainable demand for colposcopy. When the switch was made from cytology to HR-HPV 394 screening in the pilot, the demand for colposcopy increased by about 80% in the prevalence round.⁷ Had direct referral of all HPV 16/18 positive women been recommended, we estimate that referral 395 396 would increase by an additional 15-20% (Supplementary information). As expected, viral clearance 397 however was substantial (32% of women with HPV 16/18 infections and negative cytology tested 398 HR-HPV negative at the 12-month early recall, and a further 26% tested negative at the 24-month 399 recall). The immediate colposcopies in women destined to clear their infections are likely to have 400 contributed to the very high average number of colposcopies needed to detect each CIN2+ case in the ATHENA study, which evaluated a setting with immediate colposcopy of all women aged ≥ 25 401 years with HPV 16/18 infections; this number was eight.¹¹ In the English pilot, where cytologically 402 403 negative women were only referred in the presence of a persistent infection, the number of colposcopies to detect a case of CIN2+ was three (8750/2869, Table 4). 404

405

Birth cohorts vaccinated against HPV 16/18 in the catch-up programme did not start entering the
CSP until 2015, which means that our analysis is representative of an unvaccinated population.
Through cross-protection, vaccination has the potential to decrease not only the prevalence of HPV
16/18 but also of certain other HR-HPV genotypes.²⁴ As a result, the overall number of screened
women who will require triage and colposcopy will decrease. The value of using genotyping for
HPV 16/18 in the remaining persistent infections will probably decrease in line with the expected
decrease in CIN2+ lesions associated with HPV 16/18.²⁵

413

The large size and prospective protocol are key strengths of our study, as well as a population-414 415 based, routine HR-HPV based screening setting using national standards and clinical guidelines, 416 with quality assured HR-HPV testing, cytology, colposcopy, and histology. The patterns of detection of CIN2+ by genotype (Table 3) were consistent with the literature. We were limited by 417 418 having access to data from the laboratories participating in the pilot; if women moved away from 419 the catchment areas of these six laboratories, their subsequent outcomes could not be traced. 420 Nevertheless, the completeness of follow-up was high, about 95% after a referral for a colposcopy 421 and about 80% after a referral for an early recall (Figure 1). We could not directly observe the 422 outcomes of a non-genotyping protocol. The resulting post hoc nature of our analysis required us to 423 make several, albeit standard,¹¹ assumptions on infection dynamics and the prevalence of CIN in 424 women when managed following the non-genotyping protocol. Nonetheless, the sensitivity analyses showed that our conclusions were robust against a variety of assumptions. Additionally, using the 425 426 data from the same three laboratories for both triage protocols meant that the background 427 characteristics of the women, the catchment areas' screening coverage, and the cytology reading 428 practices were constant. Finally, while our study compared two defined triage protocols, it cannot 429 provide a conclusive answer as to what the optimal triage strategy would be for English HR-HPV 430 positive women. A full optimisation study would require a substantially different approach 431 comparing a number of alternative strategies, varying e.g. the eligibility criteria for triage, the 432 number of early recalls, their timing, the tests and their positivity thresholds, and any age stratification.²⁶ This is beyond the scope of our analysis. 433

434

435 CONCLUSION

436

In population based screening programmes with good quality of triage cytology and where most
women adhere to early recall, HPV 16/18 triage of persistently HR-HPV positive and cytologically

- 439 negative women 12 months after primary screening can add very little in terms of a clinical benefit
- 440 such as additional detection of CIN2+.

441

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449

450 ETHICS APPROVAL AND CONSENT TO PARTICIPATE

451 Women participating in the HPV primary screening pilot were invited to make an informed choice 452 on participating in the cervical screening programme. A decision is made to accept or decline a screening test based on access to accurate and up-to-date information on the condition being 453 screened for, the testing process and potential outcomes. Specific information was provided at the 454 455 invitation stage allowing for personalised informed choice. There was further opportunity to reflect 456 on what the test and its results might mean when they attended for screening with the clinician 457 taking the sample. Regulation 5, Health Service Regulations 2002, Confidentiality Advisory Group 458 Reference: 15/CAG/0207, was the legal basis to process the data.

459

460 CONSENT FOR PUBLICATION

- 461 Not applicable.
- 462

463 DATA AVAILABILITY

464 No additional unpublished data are available from the authors. Requests for access to data should be465 made to Public Health England, Office for Data Release.

466

467

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471	The funding for the pilot and the epidemiological evaluation thereof was provided by PHE. PHE
472	had a role in designing the pilot; in the collection of the data; and commented on the manuscript.
473	MR and HK made the final decision to submit.
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477	
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481	
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483	
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506	Study design: MR, HK
507	Data management: CM
508	Statistical analysis: MR, AB
509	Drafted the paper: MR, HK
510	Commented on the draft: all authors
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598	Effectiveness Analyses of Human Papillomavirus Testing in Cervical Screening. Value Health
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600	

- Table 1. Management of women in the English pilot of primary cervical screening with HR-HPV
- 603 testing.

Time of testing	Genotyping triage	Non-genotyping triage ^b				
Baseline test	HR-HPV negative: routine recall at 3/5 years ^a					
	HR-HPV positive/positi	ve cytology: colposcopy				
	HR-HPV positive/negative cyte	ology: early recall at 12 months				
Early recall at 12 months	HR-HPV negative: routine recall at 3/5 years ^a					
	HR-HPV positive/cytology positive: colposcopy					
	HPV 16/18 positive/cytology	HR-HPV positive/cytology				
	negative: colposcopy	negative: early recall at 24				
	Other HR-HPV positive/cytology	months				
	negative: early recall at 24					
	months					
Early recall at 24 months	HR-HPV negative: routine recall at 3/5 years ^a					
	HR-HPV positi	ve: colposcopy				

^a Depending on the woman's age. The three-year routine recall interval is used for women aged 25-49 years, whereas

605 the five-year interval is used for women aged 50-64 years.

606 ^b One of the laboratories recorded HR-HPV genotyping information using a DNA assay but did not use it for clinical

- 607 management of HR-HPV positive women.
- 608
- 609
- 610
- 010
- 611

613 Table 2. Observed outcomes for HR-HPV positive women in the three genotyping laboratories combined.

	Ν	Yes	Unknown	Proportion Yes
Baseline				
HR-HPV+	127,238	16,097	258	12.7%
Cytology+ if HR-HPV+	16,097	5287	0	32.8%
Had colposcopy if HR-HPV+/cytology+ after a record of referral	5287	5163	0	97.7%
PPV of colposcopy for CIN2+ if HR-HPV+/cytology+	5163	2135	0	41.4%
PPV of colposcopy for CIN3+ if HR-HPV+/cytology+	5163	1367	0	26.5%
Early recall at 12 months (HR-HPV+/cytology- at baseline)				
Had early recall testing after a record of referral	10,810	8964	125	83.9%
HR-HPV+	8964	5263	0	58.7%
Cytology+ if HR-HPV+	5263	1410	23	26.8%
Had colposcopy if HR-HPV+/cytology+ after a record of referral	1410	1353	0	96.0%
PPV of colposcopy for CIN2+ if HR-HPV+/cytology+	1353	473	0	35.0%
PPV of colposcopy for CIN3+ if HR-HPV+/cytology+	1353	269	0	19.9%
Cytology- if HR-HPV+	5263	3830	23	72.8%
HPV 16 or 18+ if HR-HPV+/cytology-	3830	1072	0	28.0%
Had colposcopy if HPV 16 or 18+/cytology- after a record of referral	1072	789	233	94.0%
PPV of colposcopy for CIN2+ if HPV 16 or 18+/cytology-	789	103	0	13.1%
PPV of colposcopy for CIN3+ if HPV 16 or 18+/cytology-	789	55	0	7.0%
Early recall at 24 months (HR-HPV other+/cytology- at baseline and HR-				
HPV+/cytology- at 12-month early recall)				
Had early recall testing after a record of referral	2758	2091	48	77.2%
HR-HPV+	2091	1368	0	65.4%
Had colposcopy after a record of referral	1368	1144	23	85.1%
PPV of colposcopy for CIN2+ if HR-HPV+	1144	117	0	10.2%
PPV of colposcopy for CIN3+ if HR-HPV+	1144	56	0	4.9%
Early recall at 24 months (HPV 16 or 18+/cytology- at baseline and HR-HPV+/cytology-				
at 12-month early recall) ^a				
HR-HPV+	98	73	0	74.5%

614 CIN: cervical intraepithelial neoplasia. HR-HPV: high risk human papillomavirus; any of the 14 high risk genotypes detectable by the Cobas and RealTime assays unless otherwise

615 specified. PPV: positive predictive value.

616 Gray cells: Proportions of women who adhered to the type of clinical follow-up recommended by the protocol, calculated after exclusion of category "unknown" from the
617 denominator (if non-zero). Where the "unknown" category was larger than zero, the value refers to women who had no record of referral to the type of follow-up that would be

618 expected following the recommendations; for them, we assumed that their outcomes would be the same as the outcomes among women who had the correct record of referral. All

- 619 other proportions are calculated using values in column "N" as the denominator, as there the "unknown" cells represent e.g. invalid testing outcomes (a normal occurrence in routine
- 620 screening which leads to tailored follow-up recommendations).

621 ^a Data from the fourth pilot laboratory which recorded HR-HPV genotyping information using a DNA assay but did not use it for clinical management of HR-HPV positive women.

Table 3. Observed distribution of HR-HPV infections and detected CIN2+, by HR-HPV genotype

and the woman's age.

		Age group					
		24-29	30-49	50-64	Total		
	N screened	23,864	72,833	30,541	127,238		
		(100%)	(100%)	(100%)	(100%)		
	HR-HPV genotype at						
	baseline						
HR-HPV	HR-HPV+	6709 (28%)	7646 (10%)	1742 (6%)	16,097 (13%)		
infections	HPV 16+	2111 (9%)	1588 (2%)	348 (1%)	4047 (3%)		
	Else HPV 18+	509 (2%)	541 (1%)	110 (<1%)	1160 (1%)		
	Else other HR-HPV+	4089 (17%)	5517 (8%)	1284 (4%)	10,890 (9%)		
Colposcopies	HR-HPV+	4013 (17%)	3890 (5%)	856 (3%)	8759 (7%)		
	HPV 16+	1649 (7%)	1125 (2%)	215 (1%)	2989 (2%)		
	Else HPV 18+	364 (2%)	325 (<1%)	61 (<1%)	750 (1%)		
	Else other HR-HPV+	2000 (8%)	2440 (3%)	580 (2%)	5020 (4%)		
CIN2+	HR-HPV+	1579 (7%)	1133 (2%)	147 (<1%)	2859 (2%)		
	HPV 16+	899 (4%)	475 (1%)	49 (<1%)	1423 (1%)		
	Else HPV 18+	138 (1%)	95 (<1%)	14 (<1%)	247 (<1%)		
	Else other HR-HPV+	542 (2%)	563 (1%)	84 (<1%)	1189 (1%)		
CIN3+	HR-HPV+	980 (4%)	699 (1%)	84 (<1%)	1763 (1%)		
	HPV 16+	613 (3%)	324 (<1%)	31 (<1%)	968 (1%)		
	Else HPV 18+	82 (<1%)	62 (<1%)	9 (<1%)	153 (<1%)		
	Else other HR-HPV+	285 (1%)	313 (<1%)	44 (<1%)	642 (1%)		

4 CIN: cervical intraepithelial neoplasia. HR-HPV: high risk human papillomavirus.

628 Table 4. Estimated numbers of colposcopies, high-grade CIN, and women not attending the two early recalls following the genotyping and non-

629 genotyping triage protocols, by time of testing.

Time of testing	Screening test outcome at time of testing	HR-HPV genotyping protocol			Non-genotyping protocol				
		Colposcopie s	CIN2+ (PPV)	CIN3+ (PPV)	Not attending early recall	Colposcopie s	CIN2+ (PPV)	CIN3+ (PPV)	Not attending early recall
Baseline test	HR-HPV+ and	5163	2135 (41%)	1367 (26%)		5163	2135 (41%)	1367 (26%)	
	cyt+								
Early recall at 12	Not attending				1741				1741
months	early recall								
	HR-HPV+ and	1369	479 (35%)	272 (20%)		1369	479 (35%)	272 (20%)	
	cyt+								
	HPV 16/18+ and	1020	133 (13%)	71 (7%)					
	cyt-								
Early recall at 24	Not attending				637				864
months	early recall								
	HPV+	1198	123 (10%)	59 (5%)		1728	221 (13%)	111 (6%)	
Total		8750	2869 (33%)	1769 (20%)	2378	8260	2835 (34%)	1751 (21%)	2626

630 CIN: cervical intraepithelial neoplasia. HR-HPV: high risk human papillomavirus. PPV: positive predictive value.

631

Table 5. Absolute and relative differences in the numbers of colposcopies, the numbers of detected CIN2+ and CIN3+, and in the numbers of women

		Absolute numbers per protocol									
		HR-HPV geno	typing protocol		Non-genotyping protocol						
Age (years)	Colposcopies (95% CI)	CIN2+ (95% CI)	CIN3+ (95% CI)	Not attending early recall (95% CI)	Colposcopies (95% CI)	CIN2+ (95% CI)	CIN3+ (95% CI)	Not attending early recall (95% CI)			
Total ^a	8750	2869	1769	2378	8260	2835	1751	2626			
	(8572-8924)	(2762-2973)	(1686-1851)	(2283-2475)	(8079-8444)	(2730-2937)	(1668-1832)	(2520-2731)			
24-29	4003	1588	985	1005	3780	1566	973	1137			
	(3889-4115)	(1510-1663)	(924-1046)	(945-1067)	(3658-3900)	(1489-1640)	(913-1033)	(1069-1206)			
30-49	3884	1135	701	1122	3665	1123	694	1221			
	(3765-4000)	(1068-1202)	(650-754)	(1057-1187)	(3543-3784)	(1057-1189)	(644-747)	(1150-1292)			
50-64	862	147	84	252	810	146	83	276			
	(806-918)	(124-172)	(66-102)	(221-283)	(752-867)	(123-170)	(66-101)	(242-311)			

634 not attending early recall between the two triage protocols, by age at screening.

635

Absolute differences Relative differences (genotyping protocol – non-genotyping protocol) (venes) Age (venes) ClN2+ ClN3+	ng
(genotyping protocol – non-genotyping protocol) (vs. non-genotyping protocol) Age (years) Colnoscopies CIN2+ CIN3+ Not attending	ng
Age (years) Colnesconies CIN2+ CIN3+ Not attending Colnesconies CIN2+ CIN3+ Not attendi	ng
Age (years) Corposcopies Criv2+ Criv3+ Not attenuing Corposcopies Criv2+ Criv3+ Not attenuing	
(95% CI) (95% CI) (95% CI) early recall (95% CI) (95% CI) (95% CI) early reca	11
(95% CI) (95% CI)	b
Total ^a +490 +34 +18 -248 +5.9% +1.2% +1.0% -2.3%	
(+420 to +562) $(+26 to +43)$ $(+13 to +24)$ $(-270 to -226)$ $(+4.4 to +7.7)$ $(+0.6 to +2.0)$ $(+0.5 to +1.8)$ $(-2.5 to -2.6)$	1)
24-29 +223 +22 +12 -131 +5.9% +1.4% +1.2% -3.2%	
(+174 to +277) $(+15 to +31)$ $(+7 to +17)$ $(-150 to -114)$ $(+3.4 to +14.8)$ $(+0.4 to +6.2)$ $(+0.3 to +5.2)$ $(-3.6 to -2.5)$	3)
30-49 +219 +12 +7 -99 +6.0% +1.1% +1.0% -1.8%	
(+174 to +269) $(+8 to +17)$ $(+4 to +11)$ $(-113 to -86)$ $(+4.0 to +8.4)$ $(+0.4 to +2.0)$ $(+0.4 to +2.0)$ $(-2.1 to -1.4 to +2.0)$	5)
50-64 +52 +1 +1 -24 +6.4% +0.9% +0.7% -1.8%	
$(+33 \text{ to } +74) \qquad (+0 \text{ to } +3) \qquad (+0 \text{ to } +2) \qquad (-31 \text{ to } -18) \qquad (+2.8 \text{ to } +12.3) \qquad (+0.1 \text{ to } +3.0) \qquad (+0.0 \text{ to } +2.7) \qquad (-2.3 \text{ to } -1.4) \qquad (-2.3 $	4)

636 ^a The totals as reported in Table 4. Sums by age differ slightly due to minor age-specific differences in completeness of follow-up and rounding.

637 ^b Vs. the number of HR-HPV positive cytology negative women at baseline.

638 FIGURE LEGENDS

639

- 640 Figure 1. Screening outcomes including colposcopies and detection of CIN2+ outside of the
- recommended protocol. Screening was undertaken between May 2013 and December 2014, follow-
- 642 up data were retrieved until May 2017. *Panel A*. Women with HPV 16/18 infections at baseline.
- 643 *Panel B.* Women with HR-HPV infections other than HPV 16/18 at baseline.

644

646 SUPPLEMENTARY INFORMATION

647	
648	Estimation of the additional number of colposcopies in the case of an immediate referral of all HPV
649	<u>16/18 positive women</u>
650	
651	Total number of colposcopies in the screened population (with the genotyping protocol): 8750
652	(Table 4)
653	
654	Number of HPV 16/18 positive, cytology negative women at baseline: 2914 (Figure 1)
655	
656	Attendance at colposcopy at baseline: 97.7% (observed for HR-HPV positive cytology positive
657	women, Table 2)
658	
659	Estimated needed number of colposcopies for direct referral of HPV 16/18 positive, cytology
660	negative women: 2846 (0.977×2914)
661	
662	Observed number of colposcopies in HPV 16/18 positive, cytology negative women (at any time
663	during the early recall and including colposcopies outside of the recommended protocol): 1485
664	(Figure 1)
665	
666	Difference between the estimated needed and the observed numbers: 1361 (2846-1485)
667	
668	Relative increase in the number of colposcopies: 16% (1361/8750)
669	
670	
671	
672	

673 Estimation of the numbers of detected CIN, colposcopies, and women not attending early recall in the base case analysis

Table S1. Observed data. (Note: This is the same as Table 2 in the main text, with the addition of "Code" which simplifies the calculations below.

677 "Unknown" results were excluded from the denominators in cases of referral that deviated from the recommended management protocol.)

Code	Description	Numerator	Denominator	Proportion
	BASELINE			
Ν	Number of women in the analysis	127,328	NR	NR
P1	HR-HPV+	16,097	127,328	12.6%
P2	Cytology+ if HR-HPV+	5287	16,097	32.8%
P3	Had colposcopy if HR-HPV+/cytology+ after a record of referral	5163	5287	97.7%
Q1	PPV of colposcopy for CIN2+ if HR-HPV+/cytology+	2135	5163	41.4%
Q1b	PPV of colposcopy for CIN3+ if HR-HPV+/cytology+	1367	5163	26.5%
	EARLY RECALL AT 12 MONTHS (HR-HPV+/cytology- at baseline)			
P4	Had testing at 12-month early recall after a record of referral	8964	10,685	83.9%
P5	HR-HPV+	5263	8964	58.7%
P6	Cytology+ if HR-HPV+	1410	5263	26.8%
P7	Had colposcopy if HR-HPV+/cytology+ after a record of referral	1353	1410	96.0%
Q2	PPV of colposcopy for CIN2+ if HR-HPV+/cytology+	473	1353	35.0%
Q2b	PPV of colposcopy for CIN3+ if HR-HPV+/cytology+	269	1353	19.9%
P6a	Cytology- if HR-HPV+	3830	5263	72.8%
P8	HPV 16 or 18+ if HR-HPV+/cytology-	1072	3830	28.0%
P9	Had colposcopy if HPV 16 or 18+/cytology- after a record of referral	789	839	94.0%
Q3	PPV of colposcopy for CIN2+ if HPV 16 or 18+/cytology-	103	789	13.1%
Q3b	PPV of colposcopy for CIN3+ if HPV 16 or 18+/cytology-	55	789	7.0%
	EARLY RECALL AT 24 MONTHS (other HR-HPV +/cytology- at baseline and HR-			
	HPV+/cytology- at 12-month early recall)			
P10	Had testing at 24-month early recall after a record of referral	2091	2710	77.2%
P11	HR-HPV+	1368	2091	65.4%
P12	Had colposcopy after a record of referral	1144	1345	85.1%
Q4	PPV of colposcopy for CIN2+ if HR-HPV+	117	1144	10.2%
Q4b	PPV of colposcopy for CIN3+ if HR-HPV+	56	1144	4.9%
	EARLY RECALL AT 24 MONTHS (HPV 16 or 18+/cytology- at baseline and HR-			
	HPV+/cytology- at 12-month early recall)			
P14	HR-HPV+	73	98	74.5%

Table S2. Genotyping protocol. Women with HPV 16/18 infections who remain HR-HPV+/cyt- at 12-month early recall are referred to colposcopy.

680 Women with other HR-HPV infections who remain HR-HPV+/cyt- at 12-month early recall are referred to 24-month early recall.

Time of	Screening test outcome	Colposcopies	CIN2+	CIN3+	Not attending early
testing	at time of testing				recall
Baseline test	HR-HPV+/cytology+	N*P1*P2*P3= 127328* (16097/127328)* (5287/16097)* (5163/5287) = 5163	N*P1*P2*P3*Q1= 5163* (2135/5163) = 2135	N*P1*P2*P3*Q1b= 5163* (1367/5163) = 1367	
Early recall at 12 months	Not attending				N*P1*(1-P2)*(1-P4) = 127328* (16097/127328)* (1- (5287/16097))* (1- 8964/10685) = 1741
	HR-HPV+/cytology+	N*P1*(1- P2)*P4*P5*P6*P7 = 16097* (1-(5287/16097))* (8964/10685)* (5263/8964)* (1410/5263)* (1353/1410)= 1369	N*P1*(1- P2)*P4*P5*P6*P7*Q2= 16097* (1-(5287/16097))* (8964/10685)* (5263/8964)* (1410/5263)* (1353/1410)* (473/1353)= 479	N*P1*(1- P2)*P4*P5*P6*P7*Q2b= 16097* (1-(5287/16097))* (8964/10685)* (5263/8964)* (1410/5263)* (1353/1410)* (269/1353)= 272	
	HPV 16 or 18+/cytology-	N*P1*(1- P2)*P4*P5*P6a*P8*P9 = 16097* (1-(5287/16097))* (8964/10685)* (5263/8964)* (3830/5263)* (1072/3830)* (789/839) = 1020	N*P1*(1- P2)*P4*P5*P6a*P8*P9 * Q3 = 16097* (1- (5287/16097))* (8964/10685)* (5263/8964)* (3830/5263)* (1072/3830)* (789/839) * (103/789) = 133	N*P1*(1- P2)*P4*P5*P6a*P8*P9 * Q3b = 16097* (1- (5287/16097))* (8964/10685)* (5263/8964)* (3830/5263)* (1072/3830)* (789/839) * (55/789) = 71	

Table S2. Continued.

Time of testing	Screening test outcome at time of testing	Colposcopies	CIN2+	CIN3+	Not attending early recall
Early recall at 24 months	Not attending				N*P1*(1-P2)*P4*P5*P6a*(1-P8)*(1-P10) = 10810*(8964/10685)*(5263/8964)*(3830/5263)*(1-1072/3830)*(1-2091/2710) = 637
	HR-HPV+	N*P1*(1- P2)*P4*P5*P6a*(1- P8)*P10*P11*P12= 10810* (8964/10685)* (5263/8964)* (3830/5263)* (1- 1072/3830)* 2091/2710 * (1368/2091) * (1144/1345) = 1198	N*P1*(1- P2)*P4*P5*P6a*(1- P8)*P10*P11*P12*Q4 = 10810* (8964/10685)* (5263/8964)* (3830/5263)* (1- 1072/3830)* 2091/2710 * (1368/2091) * (1144/1345) * (117/1144) = 123	N*P1*(1- P2)*P4*P5*P6a*(1- P8)*P10*P11*P12*Q4b = 10810* (8964/10685)* (5263/8964)* (3830/5263)* (1- 1072/3830)* 2091/2710 * (1368/2091) * (1144/1345) * (56/1144) = 59	
Total		8750	2870	1769	2378

Table S3. Non-genotyping protocol. All women with HR-HPV infections who remain HR-HPV+/cyt- at 12-month early recall are referred to 24-

689 month early recall (regardless of genotype).

Time of	Screening test outcome	Colposcopies	CIN2+	CIN3+	Not attending early
testing	at time of testing				recall
Baseline test	HR-HPV+/cytology+	N*P1*P2*P3=	N*P1*P2*P3*Q1=	N*P1*P2*P3*Q1b=	
		127328* (16097/127328)* (5287/16097)* (5163/5287) = 5163	5163* (2135/5163) = 2135	5163* (1367/5163) = 1367	
Early recall at 12 months	Not attending				N*P1*(1-P2)*(1-P4) = 127328* (16097/127328)* (1-(5287/16097))* (1- 8964/10685) = 1741
	HR-HPV+/cytology+	N*P1*(1- P2)*P4*P5*P6*P7 = 16097* (1-(5287/16097))* (8964/10685)* (5263/8964)* (1410/5263)* (1353/1410)= 1369	N*P1*(1- P2)*P4*P5*P6*P7*Q2= 16097* (1-(5287/16097))* (8964/10685)* (5263/8964)* (1410/5263)* (1353/1410)* (473/1353)= 479	N*P1*(1- P2)*P4*P5*P6*P7*Q2b= 16097* (1-(5287/16097))* (8964/10685)* (5263/8964)* (1410/5263)* (1353/1410)* (269/1353)= 272	
Early recall at 24 months	Not attending				N*P1*(1- P2)*P4*P5*P6a*(1-P10) = 10810* (8964/10685)* (5263/8964)* (3830/5263)* (1- (2091/2710)) = 885

Table S3. Continued.

Time of testing	Screening test outcome at time of testing	Colposcopies	CIN2+	CIN3+	Not attending early recall
	HR-HPV+	N*P1*(1- P2)*P4*P5*P6a*P10*((1- P8)*P11+P8*P14)*P12 = 10810* (8964/10685)* (5263/8964)* (3830/5263)* (2091/2710)* ((1- (1072/3830))* (1368/2091) + (1072/3830)* (73/98))* 1144/1345 = 1728 HR-HPV other: 1198 HPV 16/18: 530	N*P1*(1- P2)*P4*P5*P6a*(1- P8)*P10*P11*P12*Q4 + N*P1*(1- P2)*P4*P5*P6a*P8* P10*Q3* (1/P9)* P12= 10810* (8964/10685)* (5263/8964)* (3830/5263)* (1- 1072/3830)* 2091/2710* (1368/2091)* (1144/1345)* (117/1144) + 10810* (8964/10685)* (5263/8964)* (3830/5263)* (1072/3830)* (2091/2710)* (103/789)* (839/789)* (1144/1345)= 221	N*P1*(1- P2)*P4*P5*P6a*(1- P8)*P10*P11*P12*Q4b + N*P1*(1- P2)*P4*P5*P6a*P8* P10*Q3b* (1/P9)*P12= 10810* (8964/10685)* (5263/8964)* (3830/5263)* (1- 1072/3830)* 2091/2710* (1368/2091)* (1144/1345)* (56/1144) + 10810* (8964/10685)* (5263/8964)* (3830/5263)* (1072/3830)* (2091/2710)* (55/789) * (839/789)* (1144/1345)= 111	
			HR-HPV other: 1198*(117/1144)=123 HPV 16/18: 1085*(103/789)* (839/789)*(1144/1345) *(2091/2710)= 99	HR-HPV other: 1198*(56/1144)=59 HPV 16/18: 1084*(55/789)* (839/789)*(1144/1345) *(2091/2710) = 53	
Total		8260	2835	1750	2626