

## **HPV Triage and Test of Cure Implementation Guide**

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# HPV TRIAGE AND TEST OF CURE: IMPLEMENTATION GUIDANCE

NHSCSP Good Practice Guide No3

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# PUBLISHED BY

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# 1. INTRODUCTION

This implementation guide has been developed to aid local programmes as they introduce Human Papilloma Virus (HPV) triage and test of cure into their routine cervical screening practice.

The aetiological role of HPV infection among women with cervical cancer is now clearly established, and the use of testing for high-risk HPV in the management of low grade cytological abnormalities of the cervix is well described in the literature.<sup>1,2,3,4</sup> Following the successful completion of NHS pilots in 2001, HPV triage testing and test of cure were initially introduced into the NHS Cervical Screening Programme in six Sentinel Sites.<sup>5,6</sup> In 2010, the success of the Sentinel Sites pilots led the Advisory Committee for Cervical Screening to recommend the rollout of HPV testing throughout the English Cervical Screening Programme. The significance of HPV testing had been recognised in 2007 in the *Cancer Reform Strategy*, and in 2011 *Improving Outcomes: a Strategy for Cancer* committed the government to rolling out HPV testing across England as triage for women with mild or borderline cervical screening test results and as a test of cure for treated women.<sup>7,8</sup> The *Operating Framework for the NHS in England 2011/12* stated that commissioners should work with their local services and NHS Cancer Screening Programmes to bring this about, with a view to ensuring a more patient-centred service and major cost savings.<sup>9</sup>

This guidance is designed to support the rollout process, drawing on the experience of HPV triage gained during the initial NHS pilots, and on the insights into HPV triage and test of cure from the Sentinel Sites Implementation Project.

## 2. BACKGROUND

### 2.1 Human Papilloma Virus

There are over 100 subtypes of HPV, most of which do not cause significant disease in humans. Some subtypes (notably types 16 and 18) have been confirmed as agents causing cervical cancer and these are known as high-risk HPV (HR-HPV) types. HPV infection in most women is transient, as it is cleared by the immune system. However, for reasons that are not clear the virus persists in some women, and it is these women who are at increased risk of cervical intraepithelial neoplasia (CIN) and cervical cancer.<sup>10</sup> Almost 100% of cervical cancers contain HPV DNA.<sup>1</sup> In women with CIN, the more severe it is the more likely it is that HR-HPV infection will be present.<sup>11</sup> Women with no evidence of HR-HPV infection are extremely unlikely to develop cervical cancer in the short to medium term. Even where abnormal cytology is present it is unlikely to reflect the more severe forms of CIN (ie CIN2 or CIN3); in most cases it will be limited to mild abnormalities that regress without treatment.

### 2.2 HPV triage

HPV triage uses reflex testing for HR-HPV to manage women with cytology results that show borderline changes or mild dyskaryosis. Cervical abnormalities requiring



treatment are present in approximately 15-20% of the women who are HR-HPV positive.

Women with borderline changes or mild dyskaryosis are tested to establish which are HR-HPV positive and may thus have significant disease. They can then be referred immediately to colposcopy. Women who do not have HR-HPV are very unlikely to have significant disease so they can be reassured and returned rapidly to routine recall, avoiding the anxiety of repeat screening tests. The negative predictive value of the HR-HPV test is reported to be between 93.8 and 99.7%.<sup>12</sup>

HPV testing for triage allows colposcopy resources to be allocated more effectively. In addition, women with significant abnormalities are referred sooner for colposcopy, while those not referred can be quickly returned to routine recall, thus avoiding the waiting and anxiety associated with a clinic appointment.

With HPV triage, women attending for screening whose result shows borderline changes or mild dyskaryosis have a test for HR-HPV performed on their liquid based cytology (LBC) sample. If HR-HPV is found the woman is referred to colposcopy: if it is not, she is returned to routine screening every 3 or 5 years, depending on her age.

Women whose cytology results show borderline high grade or borderline endocervical cells should be included in the triage protocol.

### **2.3 HPV test of cure**

HPV test of cure uses HR-HPV testing of women who have been treated for any grade of CIN to assess their risk of having residual or recurrent disease. The follow up of treated women in the NHS Cervical Screening Programme (NHSCSP) has involved annual screening for up to 10 years before their return to routine recall. However, it is now known that women who have normal cytology and are negative for HR-HPV at their follow up screening appointment are at very low risk of residual disease and need not be recalled for their next screening appointment for a further three years.<sup>13</sup>

Test of cure means that if the cytology result following treatment is normal, mild or borderline a test for HR-HPV will be performed. If the test is negative the woman will not be recalled for a further three years. If HR-HPV is found, however, she will be referred again to colposcopy and followed up in accordance with national guidelines. By employing the HPV test of cure approximately 80% of treated women avoid having to undergo annual cytology tests.

Women who have received treatment for CGIN or for invasive disease are excluded from the test of cure protocol.

### **2.4 HPV pilots and the Sentinel Sites Implementation Project**

The HPV triage pilots of 2001 demonstrated that the introduction of HPV triage in the NHSCSP was feasible, acceptable to women and cost effective.<sup>6,14</sup> However, it saw a large initial increase in the number of referrals to colposcopy. These declined somewhat after 6–12 months but without returning to the earlier lower levels. This increased demand for colposcopy resources sustains the increased sensitivity of the programme.

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The introduction of HPV triage into the programme was carefully organised and monitored in the six Sentinel Sites in order to manage the impact on colposcopy services. As intended,<sup>15</sup> this experience is being built on now as implementation is extended to the rest of England. Demand during the early stages is being managed as follows

*Year one*

- HPV testing for triage should be conducted only on the first occurrence of a borderline or mild sample in eligible women routinely invited for screening
- test of cure should be restricted to women returning for their first post treatment test (six months), who have normal, borderline or mild cytology

*Year two*

- testing for triage should be extended to all borderline and mild samples
- test of cure should be extended to all women treated for CIN who have normal, borderline or mild cytology at their next annual follow up test.

Programme funding will be structured to reflect this implementation plan.

The Sentinel Sites experience demonstrated that it was possible to implement HPV triage and, in the light of emerging evidence, enabled the HPV test of cure to be introduced for women who had been treated for CIN. It also indicated that cost savings associated with these strategies would be realised from year three.<sup>14</sup> Above all, it highlighted the potential of HPV triage and test of cure to reduce dramatically the time spent on diagnosis and treatment. The scale of this reduction is illustrated in Figure 1 below.

**Figure 1** A woman with CIN 3, (a) with and (b) without HPV triage and test of cure

(a) HPV triage and test of cure	(b) Standard treatment
<ul style="list-style-type: none"> <li>▪ Routine screen</li> <li>▪ Borderline cytology, HPV+</li> <li>▪ Colposcopy at 8 weeks from date of test</li> <li>▪ CIN3 detected</li> <li>▪ Treated with LLETZ</li> <li>▪ Test of cure at 6 months, negative</li> <li>▪ 3 year recall</li> <li>▪ Time for whole episode: 9 months</li> </ul>	<ul style="list-style-type: none"> <li>▪ Routine screen</li> <li>▪ Borderline cytology</li> <li>▪ Repeat at 6 months, borderline cytology</li> <li>▪ Repeat at 6 months, borderline cytology</li> <li>▪ Colposcopy 14 -18 months from date of initial test</li> <li>▪ CIN 3 detected</li> <li>▪ Treated with LLETZ</li> <li>▪ Annual follow up for 10 years</li> <li>▪ Time for whole episode: 12 years</li> </ul>

### 3. IMPROVEMENTS TO THE PROGRAMME AND COST SAVINGS

The implementation of HPV triage and test of cure has brought a number of clinical benefits to the cervical screening programme. There is more rapid identification of high grade CIN and increased specificity in women undergoing HPV triage when compared with cytology.\* In addition, women with abnormal test results have shorter patient journey times and there is rapid resolution of uncertain screening episodes by reaching a definitive endpoint. The HPV test of cure offers faster return to recall for treated women.

Although cost saving is not the primary consideration, these improvements to the programme do offer substantial savings once the initial two years following implementation have passed. In women with borderline changes, HPV triage results in the same referral rate but a better selection of cases overall. In women with mild dyskaryosis, only 14% of women will not be referred to colposcopy in laboratories that refer on first mild; the same referral rate but with better selection of cases will occur in laboratories that refer on second mild.

The main costs associated with implementing HPV triage and test of cure are the HR-HPV tests themselves (which cost in the region of £15-20 each, depending on screening scale and the platform chosen) and the transporting of samples for HPV testing to the test centre.

Reduced repeat testing in women with borderline changes or mild dyskaryosis will result in cost savings to primary care and laboratories. The number of women invited in 2009-10 due to a previous abnormality was 175,984, potentially saving £6,159,440 by year 5 of implementation at a cost of £35 per invitation.\*

The rate of women failing to arrive at colposcopy was reduced from approximately 20% to 10% in the Sentinel Sites. If repeated across the English programme as a whole, this could avoid approximately 17,600 missed appointments per annum.

Managing treated women using the HPV test of cure enables 75% of them to be discharged at six months following treatment, rather than after up to 10 years of annual cytology. These women will then return for two or three routine screenings in the following 10 years, depending on age. There were 642,756 women in follow up after treatment having annual cytology in 2009-10. Therefore, this figure could be reduced by two thirds to around 214,000 per year. With a cost of £35 per screening, this would generate a potential saving of  $428,756 \times £35$ , or £15,006,460 per annum

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\* The cost projections and other figures in Section 3 are based on experience gained during the Sentinel Sites Implementation Project.<sup>6</sup>

## 4. ROLLOUT

### *Rollout planning*

From 2011/12, NHS commissioners in England are expected to work with local services and NHS CSP to implement HPV triage across the remainder of the NHSCSP for women with mild or borderline results.<sup>8,9</sup>

Each SHA is asked to consider the options for local application and present its plans to the National Office of the NHS CSP for approval

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Criteria against which bids will be assessed include

- size of laboratory (each laboratory must ideally be reporting a minimum of 35,000 samples per annum when implementation starts; those that are not should have local plans in place to report a minimum 35,000, as this is likely to optimise the cost savings of HPV triage and test of cure)
- sufficient and sustainable colposcopy capacity
- currently achieving, and able to maintain, 14 day turnaround
- quality, and EQA compliance, of HPV testing arrangements
- developed proposal for a suitable training programme for local professionals
- identification of a pathway manager to oversee all aspects of delivery (see Appendix 1 for a description of this role)
- QA and PCT support for the bid
- ability to start HPV testing in financial year 2011/12.

Central funding will be available to support the first two years of implementation, as outlined in Appendix 2.

### *Preparation for rollout*

It is essential that all elements of the local programme are engaged well in advance of implementation. Between three and six months should be built in to any proposal to allow for this.

- The HPV test platform must be chosen (see section 7).
- A start date must be agreed between all elements of the local programme to ensure that the cytology laboratory is not required to use separate protocols for different populations of women.
- Sufficient colposcopy capacity must be in place.
- Training must be provided for staff involved in the delivery of HPV testing, including primary care staff and other sample takers, laboratory and colposcopy staff (see section 10).
- The call/recall office must be engaged at an early stage to ensure that they are ready to set up IT system changes to support new codes and issue the first invitations six weeks in advance of the start date, along with appropriate

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patient information (see section 13.2). A diagram showing the HPV action and result codes to be introduced can be found at Appendix 3.

- All programmes should be alert from the outset to the full implications for local IT processes of implementing HPV triage and test of cure. Guidance for users of the NHAIS system will be published alongside this document on [the NHSCSP intranet site](#).
- The new nationally-produced information leaflets appear at Appendix 4. Templates for the new patient letters associated with each result code can be found on [the NHSCSP intranet site](#).
- Local protocols must be rewritten to reflect all of these changes.

Where implementation is staged, GP practices that are not yet involved in testing, but straddle other programme areas that are, should be alerted to the possibility of being contacted by patients about HPV testing. (This should cease to be an issue after a few months.)

## 5. SAMPLES

HR-HPV testing is performed on the same LBC sample that is taken when a woman attends for cervical screening. The sample requirements will depend on the LBC technology and the HPV test used.

If a woman's sample is unsuitable for HPV testing for any reason (eg it includes insufficient material) she should be managed on the basis of cytology alone.<sup>17</sup>

## 6. HPV TESTING CENTRES

For HPV testing to be cost-efficient and meet the 14-day turnaround time, testing needs to be performed sufficiently often at dedicated centres with enough throughput to meet the required timescales.

In the Sentinel Sites Implementation Project additional savings were made by reducing the administration in transporting samples between laboratories (see section 8).

## 7. HIGH-RISK HPV TESTS

There are a number of HR-HPV test platforms available in the UK, all of which test for 16, 18 and a range of other high-risk sub-types. NHSCSP is currently analysing CE-marked tests manufactured by Roche, Abbott, GenProbe and Hologic to assess their suitability for use in the cervical screening programme and their performance when compared with the Qiagen Hybrid Capture 2 test. Details of tests considered suitable for HPV triage and test of cure in the NHSCSP will be published on its [intranet site](#) in Autumn 2011.

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## 8. TRANSPORTATION OF SAMPLES TO THE HPV TESTING CENTRE

Samples requiring HPV testing can be transported at ambient temperature.<sup>17</sup>

In the Sentinel Sites Implementation Project, samples were transported from cytology laboratories to HPV testing centres by local courier. The cost of this depended on the distance between the Site and the HPV testing centre, with average costs for approximately 50km of £0.44 per sample.<sup>§</sup>

All samples to be processed off-site must be packaged in compliance with IATA packaging instruction 650 and UN3373 (Diagnostic Specimens).<sup>18,19</sup> SurePath LBC vials and tubes must be given replacement lids before packing, to prevent leakage. Guidance and Standard Operating Procedures covering these and other aspects of packaging and transport appear at Appendix 5.

## 9. QUALITY ASSURANCE OF HPV TESTING

HPV testing within the NHSCSP must be undertaken in CPA accredited facilities.<sup>20</sup> Laboratories implementing HR-HPV testing must be able either to show experience in interpreting and troubleshooting with molecular technologies or to demonstrate collaboration with an accredited laboratory experienced in molecular diagnostics.

It is also expected that cytology laboratories carrying out tests will have strong links with virology colleagues, to facilitate high-quality testing and support the effective management of more challenging cases.

The HPV test used must be chosen from those considered acceptable for use within the NHS CSP. All laboratories providing HPV testing must participate, and show adequate performance, in an accredited external quality assurance scheme such as the UK NEQAS scheme for HPV,<sup>21</sup> The scheme includes 5 unknown samples three times per year and the cost of participation is currently around £500 per annum. Other schemes include QCMD-HPV (an analytical scheme for quantification assays) and WHO HPV LabNet (currently restricted and more relevant for HPV typing and epidemiology than screening).

All laboratories providing HPV testing must include positive and negative internal quality control (IQC) samples as well as all required kit controls in every run. IQC samples should be prepared in sufficient volume to permit repeated testing to check the reproducibility of results. It should be appreciated that this can add 10-15% to the number of tests performed. The use and recording of IQC sample results must comply with CPA standard F3.

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<sup>§</sup> Figures based on experience gained during the Sentinel Sites Implementation Project and NHS Cancer Screening Programmes draft projection (2011) for rollout of HPV triage.

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## 10. TRAINING

The implementation of HPV triage and test of cure places special demands on a range of staff, in particular

- a) primary care staff taking samples and counselling women
- b) laboratory and cervical cytology laboratory staff undertaking HPV testing
- c) cytology laboratory staff involved in HPV testing
- d) colposcopists receiving HPV referrals.

The training required to meet these demands successfully is outlined below. Further details can be found at Appendix 6.

### 10.1 Primary care

Engaging primary care is crucial if HPV triage and test of cure are to be successfully implemented. During the Sentinel Sites Implementation Project several training models were used to provide sample takers with information about HPV, protocols and management practices. A national primary care information pack was developed to support these initiatives (see 13.1). It is recommended that this information be included as part of a formal update course for sample takers.

Initial sample taker training may be delivered face-to-face (eg at seminars), by post (with material mailed to individuals) or online. At some Sentinel Sites training events were provided by senior laboratory staff. In some cases these events were open to all sample takers; in others, at least one sample taker from each GP practice was required to attend and cascade the information to all other sample takers in the practice. In one Sentinel Site two local events were held, after which any GP practice without representation at either meeting was visited. One Site chose to mail out the primary care information packs, following this with two question-and-answer sessions for sample takers.

Experience from the Sentinel Sites Implementation Project has underlined the importance of maintaining effective communications with primary care staff throughout the implementation process. One issue encountered by all Sites was the large number of inappropriate early repeats among women who had undergone HPV triage, tested HR-HPV negative and been returned to routine recall. The samples yielded by these early repeats should not be tested; instead, correspondence should be sent to the sample taker explaining that an inappropriate test has been taken.

All primary care staff should be asked to confirm that they have understood the changes to the programme and will be able to counsel women appropriately.

### 10.2 Cytology laboratory staff

All staff involved in screening and reporting cytology samples for HPV testing should undergo training. Packaging tests and data transcription protocols, quality control and health and safety will all form part of routine departmental training. In addition, the National Cervical Cytology Education and Training Committee (NCCETC) recommends a half-day course at an approved cytology training centre. Consultants, ABMSPs/BMS consultants, BMSs and all screening staff are required to attend, and attendance is mandatory for at least one consultant and one laboratory manager from each cytology laboratory site.



An indication of course content appears at Appendix 6. The lead consultant must confirm in writing that the course's content has been cascaded to all pathologists, BMSs and cytology screeners.

### **10.3 Laboratory staff**

All staff involved in handling samples for HPV testing should undergo training. If more than one or two bench staff are involved this training should be undertaken on-site by competent individuals. It should include following the relevant protocols and the correct placing of samples. Guidance and example protocols for staff who package samples for analysis off-site can be found at Appendix 5. Staff transferring HPV test results to spreadsheets or databases will also need an explanation of protocols, as well as training in database use and quality control (eg avoiding transposition errors).

All staff performing HPV testing must have received enough training to undertake the procedure competently. It is anticipated that instruction in the test technique and in troubleshooting will be provided by the test manufacturer. This instruction will be subject to review, to ensure compliance with NCCETC recommendations. Local training can then be cascaded as necessary and recorded in training logs, as required by CPA. (See Appendix 6.) The World Health Organization's *Human Papillomavirus Laboratory Manual* is a useful additional resource.<sup>22</sup>

### **10.4 Colposcopy staff**

It is crucial to engage with and train colposcopy staff before implementation. This training may take place alongside primary care colleagues or in a separate training initiative. The course programme will be agreed by the NHS CSP's Colposcopy Quality Assurance Group and British Society for Colposcopy and Cervical Pathology (see Appendix 6.)

Colposcopy staff will often be the first point of contact in the NHSCSP for women who receive a positive HR-HPV test result and they may therefore need to provide information and counselling. In addition, the HPV triage and test of cure management protocol directly affects the management of women at colposcopy. These developments call for changes to existing protocols, as well as the inclusion of appropriate information on discharge letters (see examples at Appendix 4).

## **11. PROTOCOLS**

### **11.1 Laboratory protocols**

Cervical cytology laboratories will require specific protocols to describe the sample processes required for HPV triage and test of cure, as well as the management of women following a positive or negative HR-HPV test result. These protocols should comply with the guidance issued by CPA.<sup>20</sup>

Laboratories should cease using terms such as 'HPV' and 'koilocytosis' to describe features in cytology reports as they may cause uncertainty about whether a woman has had an HPV test and the test's outcome. However, laboratories may record these features elsewhere for internal audit purposes.

HPV triage samples should be confirmed as borderline changes or mild dyskaryosis by a pathologist or ABMSP before submission for HPV testing. It is acceptable for BMS staff to add HPV test results after a pathologist or ABMSP has issued an abnormal cytology report. This will include adding the management recommendation and authorising the cervical screening reports in accordance with the HPV triage and test of cure management protocol.

A single final report should be issued that includes cytology, HR-HPV status, and management code, eg

Mild dyskaryosis (result code: M)  
HR-HPV detected (infection code: 9)  
Direct referral for colposcopy (action code: S)  
(Final code combination: M9S.)

Data security should be protected at all times. Particularly where HPV results will be transmitted from one laboratory to another, methods such as the National Pathology Exchange are recommended as these allow test requests and results to be exchanged rapidly, robustly and with minimal transcription. Transmission by nhs.net is secure and acceptable, however. Protocols must meet local needs and comply with the recommendations of the National Information Governance Board for Health and Social Care.<sup>23</sup>

## 11.2 Management of women

Figure 2 below shows the mandatory protocol for managing women in the NHSCSP with the introduction of HPV triage and HPV test of cure. (Refer also to section 11.2.4 on the phased implementation of test of cure.)

### 11.2.1 HPV test result unavailable at triage

There will be occasions when an HPV test result is not available at triage: eg when an inadequate cytology sample has been found to contain abnormal cells but its cellular content is insufficient for high-risk HPV testing. In such cases, if the cytology result is mild dyskaryosis the woman should be referred to colposcopy. If the result is borderline, a six month repeat cytology sample should be requested. An HPV test should be performed at six months if the cytology result is normal, borderline or mild dyskaryosis. If the woman is HR-HPV negative she should be returned to routine recall; if HR-HPV positive, she should be referred to colposcopy. Any cytology of moderate dyskaryosis or worse should receive a colposcopy referral without HPV testing.

### 11.2.2 Women with untreated CIN1

Women with biopsy-proven untreated CIN1 (whether it arises from a low or high grade index cytology sample) will be managed by cytology at 12 months with or without colposcopy, depending on local practice. If cytology is borderline, repeat HPV triage. If it is not, follow up of 12 month cytology alone should be in accordance with normal NHSCSP protocols.

Women who default from colposcopy should be referred once again when they have their next cytology test, regardless of the test result. In these circumstances no HPV test is required.

### 11.2.3 Women under the age of 25

Women under the age of 25 should not be screened as part of the NHSCSP and are therefore ineligible for HPV triage.\* However, as first screening invitations may be sent up to six months in advance of a woman's 25<sup>th</sup> birthday, those who are invited for screening and attend before their birthday will be included.

### 11.2.4 HPV test of cure

In year one the HPV test of cure will be implemented immediately and used initially for women treated in the months prior to implementation, that are now returning for their first follow up test at six months.

When a local programme has completed its first year and fully implemented HPV triage, the test of cure element of the protocol should be extended to all treated women. It will apply to all women attending their first post-treatment follow up appointment or cytology test, irrespective of the grade of treated CIN, and all women in annual follow up after treatment for CIN (wherever they are in the 10-year surveillance process).† These women will then be managed in the same way, in accordance with the test of cure protocol.

All women entering the test of cure who have normal, borderline or mild cytology and are HR-HPV negative will be invited for their next cytology test in three years, regardless of their age. If at three years their cytology result is negative, women aged over 50 years should revert to their normal recall pattern (ie every five years). Women with moderate or worse cytology, whatever their age, will be referred to colposcopy.

If a woman fails to attend colposcopy following treatment and returns to the care of her GP before her first follow up cytology, she should still be included in the test of cure protocol.

A woman will be referred to colposcopy if test of cure shows borderline changes or mild dyskaryosis or normal cytology and she is HR-HPV positive. If the colposcopy is satisfactory and negative she can be recalled in three years (see Appendix 7).

Women who reach 65 must be invited for screening until the protocol is complete, and otherwise comply with national guidance. Women aged over 60 who have borderline changes or mild dyskaryosis and test HR-HPV negative at triage can be ceased from the NHSCSP, as their next test-due date would be after age 65. Women aged over 60 who have mild, borderline or normal cytology and are HR-HPV negative at test of cure will return for a further cytology test three years later, regardless of whether or not they will be aged over 65 when that test is due. Only if this further cytology test is normal can they be ceased from the programme.

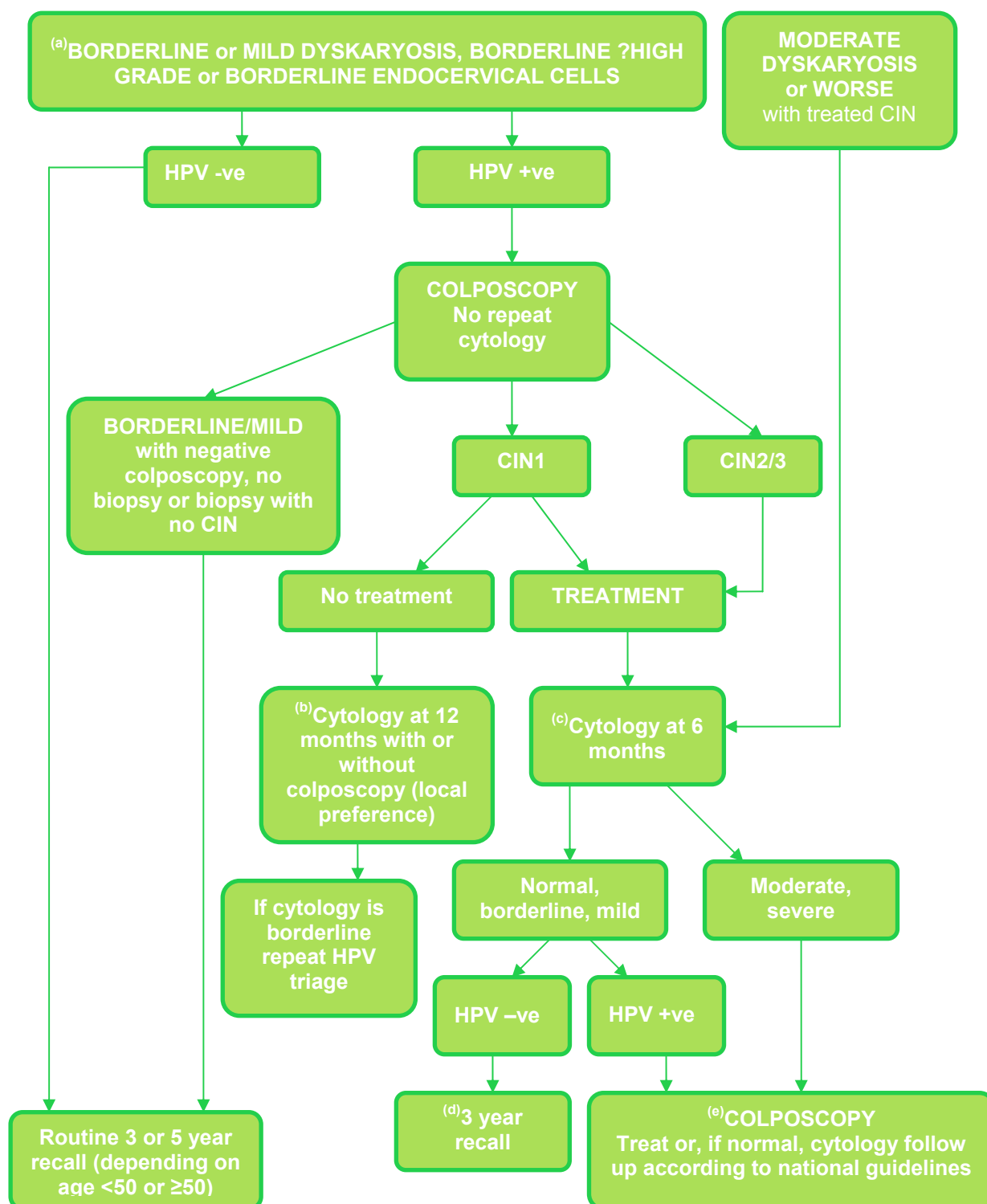
If a woman under the age of 25 has received treatment for CIN she can be included in the HPV test of cure at her follow up appointment, regardless of her age.

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\* Also ineligible for HPV triage are women resident in England but first screened in Wales or Scotland (where invitations begin at age 20) who are reinvited automatically for cervical screening by the NHAIS system at ages 21–24.

† The test of cure protocol will not apply to women who have received treatment for CGIN or who have invasive disease (see section 2.3).

**Figure 2** HR-HPV triage and test of cure protocol for the management of women aged 25-64 in NHS CSP



#### NOTES

**(a)** If sample is unreliable/inadequate for the HPV test, refer mild and recall borderline for 6 month repeat cytology. At repeat cytology HPV test if negative/borderline/mild. If HPV negative return to routine recall: if HPV positive, refer. Refer moderate or worse cytology. **(b)** Follow up of 12 month cytology only should follow normal NHSCSP protocols. **(c)** Women in annual follow up after treatment for CIN are eligible for the HPV test of cure at their next screening test. **(d)** Women  $\geq 50$  who have normal cytology at 3 years will then return to 5 yearly routine recall. Women who reach 65 must still complete the protocol and otherwise comply with national guidance. **(e)** Women referred owing to borderline or mild or normal cytology who are HR-HPV positive and who then have a satisfactory and negative colposcopy can be recalled in 3 years.

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## 12. LABORATORY IT SYSTEM CHANGES

### 12.1 Changes to local laboratory IT system software

Changes may need to be made to local laboratory IT system software to allow the recognition of HPV test result codes. Where possible, these changes should be made at a national system level, for all users.

Laboratories sending HPV-tested results will need to be able to use the following result codes

- M (mild dyskaryosis)
- B (borderline changes)
- N (negative cytology)

and the following infection codes

- Ø (HPV negative)
- 9 (HPV positive)
- U (HPV unavailable/unreliable).

If the laboratory computer system also validates result/infection/action code combinations, then it will be necessary to ensure that the system will also accept the code combinations required for HPV triage and test of cure.

### 12.2 Planned changes to NHAIS (Exeter) coding protocols

For planning purposes, programmes may wish to note that changes are being made to NHSCSP terminology and will be reflected in new NHAIS (Exeter) codes. These code changes are likely to be implemented in 2012 or 2013, and are as follows.

- the addition of result code 0 for 'abnormal, not cervical' (eg endometrial)
- the addition of result code 9 for 'borderline glandular (not HPV tested)'
- the addition of result code G for 'borderline glandular (HPV tested)'
- the changing of 'moderate' to 'HSIL (moderate)'
- the changing of 'severe' to 'HSIL (severe)'
- the changing of 'mild' to 'LSIL'.

There will also be new algorithms for 0 and 9/G, but no new action codes will be required.

**Until formal notification of these changes is issued, the existing terminology and codes should continue to be used.**

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## 13. INFORMATION MATERIALS

### 13.1 Primary care information pack

An HPV triage and test of cure primary care information pack is available to all sample takers in the NHSCSP. It provides appropriate information to help them advise and counsel women who have had an HPV test, or may go on to have one. Copies of this pack are available free of charge to NHS staff via the Department of Health publications orderline (see Appendix 8) and individual items can also be downloaded from [the NHSCSP intranet site](#). It is recommended that local primary care HPV training be based on the pack and that copies of it are distributed at HPV training events.

The information pack comprises

- a leaflet for sample takers on HPV testing
- a leaflet for women on HPV testing
- a list of frequently asked questions
- a leaflet on HPV implementation
- a copy of the cervical screening leaflet sent to every woman with her invitation
- a flowchart of the new protocol and management system for women having an HPV test
- a DVD containing a PowerPoint training presentation on HPV triage and test of cure.

The first three of these are reproduced in Appendix 4.

### 13.2 Standard invitation and result letters

The introduction of HPV triage and test of cure will call for a new set of standard invitation and results letters. Call/recall offices send most correspondence to women and (as noted in section 4) they must be engaged from the outset in implementation arrangements. Before the new protocols begin, HPV software enhancements must be activated at each site by NHS Connecting for Health. A number of system parameters must also be set and tested before the first HPV results are received from the laboratory. To ensure that information sent out to women is correct and appropriate, the text of existing invitation and result letters must be reviewed and additional result letters set up for the new result/infection/action code combinations. Information on the letters and codes to be used appears at Appendix 4. Screening department staff implementing HPV triage and test of cure may find it useful to visit sites already using the software enhancements. Further information and guidance can be obtained from the National Office of the NHS CSP ([www.cancerscreening.nhs.uk](http://www.cancerscreening.nhs.uk)).

### 13.3 Information for women

All women invited for cervical screening need to receive information about HPV along with their invitation, as the NHSCSP cannot predict which of them will go on to have an HPV test.

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HPV testing is offered to women as part of an enhanced screening service. This means that individual consent to the additional test is not needed. It is the sample taker's responsibility to ensure that the woman to be tested has received all the necessary information and understood it. Once this is confirmed, her consent to HPV testing is implied (as with cervical screening) by the fact that she has attended and accepted the procedure. A separate information leaflet has been developed for inclusion (with the NHSCSP leaflet *Cervical Screening: The Facts*) in all invitation and reminder letters for routine call and recall tests and early recall tests (see Appendix 4). Similarly, any routine invitation letters that are not sent by call/recall offices (eg invitations sent by GPs or laboratories) must include the HPV leaflet. It will also need to be sent out with all screening invitations for a period of six weeks before the introduction in a laboratory of HPV testing protocols, to ensure that women attending for screening receive it by the start of implementation.

The HPV information leaflet must also be sent to women who have received treatment for CIN, as they may be eligible for the HPV test of cure at their six month appointment for follow up cytology. These women often receive their next appointment directly from the colposcopy unit, so copies of the leaflet will need to be included in the correspondence.

As noted in 13.1 above, the English version of the HPV leaflet for women can be obtained from the Department of Health publications orderline (see Appendix 8) and is reproduced in Appendix 4. It has also been translated into a number of other languages, and these versions are available to download as PDF documents from the NHS CSP website ([www.cancerscreening.nhs.uk](http://www.cancerscreening.nhs.uk)).

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## APPENDIX 1 Pathway manager: outline description of role

With the implementation of HPV triage and test of cure, each local screening programme is required to develop an identifiable network comprising call/recall offices, colposcopy clinics and laboratory services to support effective delivery. A pathway manager will be identified to optimise its operation. This will usually (but not necessarily) be in the network's lead acute trust.

The pathway manager's role will be to

- oversee all aspects of the delivery of the cancer screening pathway
- ensure the integration of the elements and organisations that make up the pathway
  - call/recall agencies
  - primary care
  - cytology/histology laboratories
  - colposcopy clinics
  - IT support
  - staff training
- work across organisational and professional boundaries to address challenges, exploit opportunities, and secure the aims and objectives of the pathway
- engage clinical, professional and other colleagues to optimise the quality and transparency of delivery and improve outcomes, in accordance with national policy and NHSCSP standards, guidelines and quality assurance arrangements
- ensure that women whose samples are processed through the laboratory services of the network follow the appropriate care pathway in a timely manner and to the correct quality standards.

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## APPENDIX 2 Funding of HPV triage and test of cure

Implementation of HPV triage and test of cure will be funded centrally, with the National Office of NHS CSP acting as commissioner and fund-holder.

Funding will cover all transition costs, including laboratory services, test kits, staff training, and enhanced colposcopy and histology provision during the implementation period.

Services will be supported for the first two years, as follows

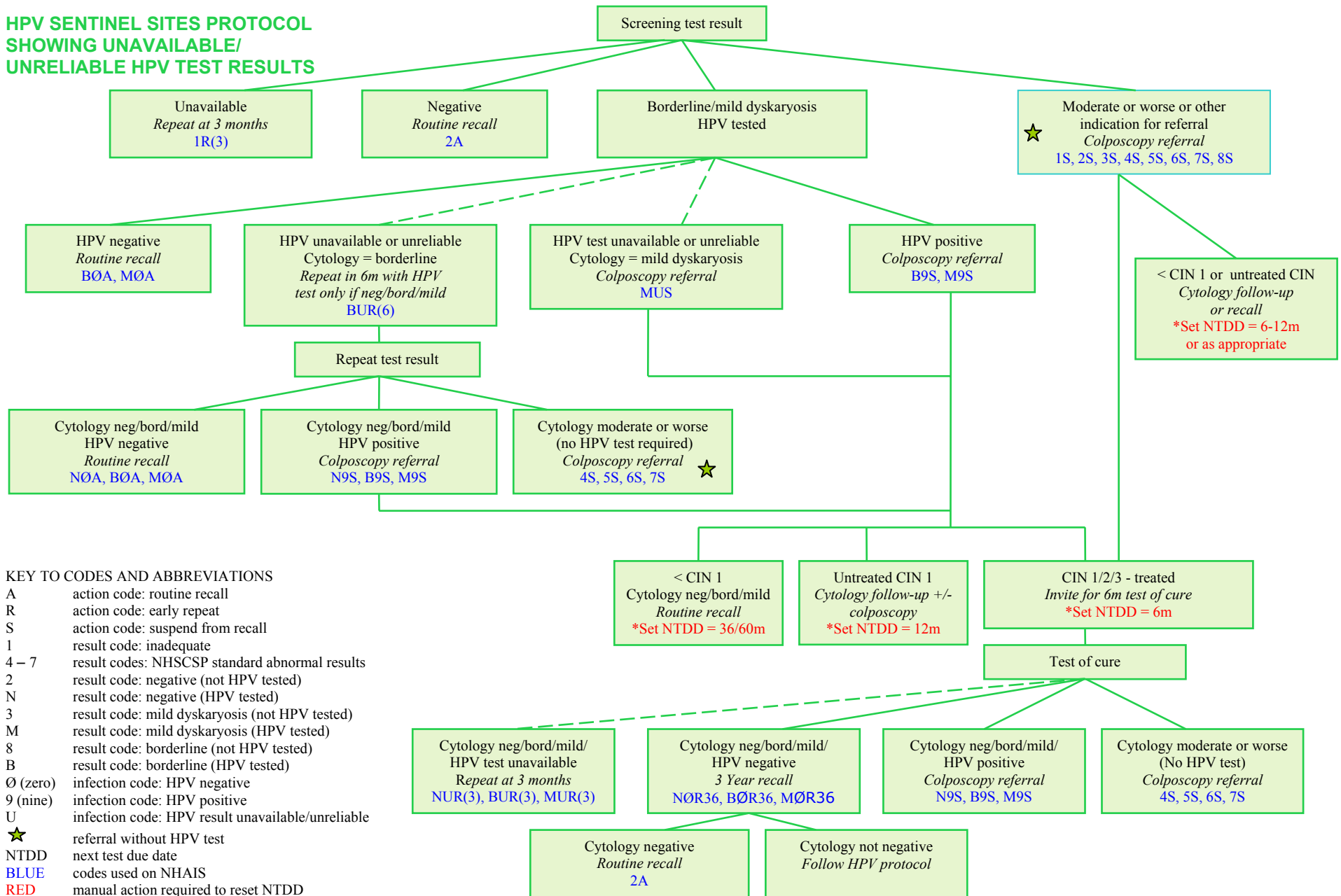
Year 1            £2 per cytology sample reported in women aged 25 and over

Year 2            £1 per cytology sample reported in women aged 25 and over

This transition funding will cover samples from GP and community clinics, hospitals and GUM services. Samples from women under 25 and non-NHS sources will be excluded.

Once the two-year rollout period is complete, funding will devolve to other bodies as part of routine NHS commissioning processes.

**HPV SENTINEL SITES PROTOCOL  
SHOWING UNAVAILABLE/  
UNRELIABLE HPV TEST RESULTS**



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## APPENDIX 4 Information leaflets, result codes and letter templates

The revised information leaflets (for sample takers and for women) and list of frequently asked questions appear below.

The full list of result codes, along with templates for the new patient letters associated with each of them, is available via a link on the homepage of [the NHSCSP intranet site](#).



# NHS Cervical Screening Programme

## HPV triage of borderline and mild dyskaryosis and HPV test of cure

### Information for sample takers

This factsheet is designed to inform sample takers and help them to counsel women who are having an HPV test as part of the NHS Cervical Screening Programme. **It is important to note that 95% of screened women will not require an HPV test.**

#### What is Human Papilloma Virus (HPV)?

There are around 100 subtypes of HPV. Most do not cause significant disease in humans. However, some subtypes (most notably subtypes 16 and 18) have been confirmed as agents causing cervical cancer. Unlike subtypes 6 and 11 (which cause genital warts) these 'high-risk' types do not produce visible symptoms.

Almost all cervical cancers contain HPV DNA. Looking at cases of CIN, we find that the higher the grade of CIN the more often high-risk HPV infection is found. This suggests that women showing no signs of infection with high-risk HPV are extremely unlikely to develop cervical cancer in the short to medium term. Even if a woman does have abnormal cytology, it is unlikely to reflect CIN2 or 3; in most cases it will be a result of low-grade abnormalities that regress without treatment.

Infection with high-risk HPV is common, especially in women under 35. In most cases the infection is transient. However, for reasons that are not yet known around 20–30% of women do not clear the infection. This group is at most risk of CIN that may eventually develop into cervical cancer.

#### How do women get the virus?

As far as we know most cases of high-risk HPV infection are sexually transmitted. HPV is easily transmitted during sex between men and women and with same-sex partners.

However, there are two important factors to bear in mind

- the infection is asymptomatic, so it may have been present and undetected for many years and have nothing to do with a woman's current relationship
- a partner may have acquired an asymptomatic infection with no visible lesions many years earlier and passed it on unknowingly.

Women can therefore be reassured that a positive test result for high-risk HPV types need not imply infidelity or promiscuity by either partner.

#### Why are we using HPV testing?

HPV testing is designed to speed up referral to colposcopy, avoid referral for those who do not need it, and allow treated women to proceed to a three year recall period after just six months.

It is well known that the cytology tests of some women with CIN3 show only low-grade abnormalities. Referral to colposcopy is usually made following persistent borderline or mild abnormalities. HPV testing aims to identify which of these women may have significant disease; they can then be referred immediately to colposcopy.

Before the introduction of HPV triage, a single abnormal cytology test result could delay a woman's return to routine screening for up to two years. However, women known to be high-risk HPV negative are very unlikely to have

significant disease. They can thus be reassured and returned immediately to routine recall without the anxiety of repeat screening tests and possible referral to colposcopy.

The follow up of treated women may involve annual cytology screening for 10 years before they return to routine recall. The HPV test of cure can avoid the need for this by helping to assess the risk of residual disease in women with normal, borderline or mild cytology. Women are tested for high-risk HPV six months after their treatment, allowing high-risk HPV negative women with normal, borderline or mild cytology to return to a three year recall period.

### How is the test done?

HPV testing is performed on the sample taken for the cytology test, so there is no need for the woman to be called for a second test.

Samples will be processed at the laboratory and all results will be issued as part of a single cytology report. A cytology report will include a result and a management recommendation, as happens now. If the result shows high-risk HPV this will be included in the report and reflected in the management recommendation.

### How will HPV testing affect women?

#### Triage

Women whose cytology test shows moderate dyskaryosis or worse will not have an HPV

test. They will simply be referred to colposcopy, as happens now.

Women whose cytology test result is negative will not have an HPV test. Depending on their previous history, they will be advised either to return to routine recall or to have an early repeat test, as at present.

Women whose cytology test shows borderline change or mild dyskaryosis will have a high-risk HPV test. If it is positive they will be referred to colposcopy. If it is negative they will return to routine three or five year recall, depending on their age.

### Test of cure

All women who have been treated for CIN will have a cytology test six months after their treatment. If cytology is normal, borderline or mild a high-risk HPV test will be performed. Women who are high-risk HPV negative will return to routine three year recall. Women who are high-risk HPV positive or have moderate or worse cytology will be referred back to colposcopy.

### Does the HPV test affect colposcopy?

The HPV test focuses on which women will go to colposcopy, which can go back to routine screening, and which can proceed to a three year recall period following treatment. At colposcopy, women's clinical management will depend (as now) on the opinion of the colposcopist who examines the cervix.



## Cervical Screening Programme

# NHS Cervical Screening Programme

## HPV testing

### Information for women

#### What is the NHS Cervical Screening Programme?

The Cervical Screening Programme aims to reduce the number of women who develop invasive cervical cancer and the number of women who die from it. It does this by regularly screening women between the ages of 25 and 64, so that conditions that might otherwise develop into invasive cancer can be identified and treated. The introduction of HPV testing will help it to do this even more effectively.

#### What is HPV?

HPV stands for Human Papilloma Virus. It is a very common infection and most women get it at some time in their life. In most cases it clears up by itself without the need for treatment.

There are many types of HPV. Most are harmless but some can cause abnormalities in the cervix and are known as 'high-risk' HPV types. These abnormalities often clear up without treatment when the virus clears. But in some women the virus persists, placing them at greater risk of developing cervical abnormalities (CIN) which may need treatment.

#### How do people get HPV?

HPV is a very common infection among people who have been sexually active at some time in their life. It is easily transmitted during sex between men and women and between partners of the same sex. The virus shows no symptoms, so it is possible that

- someone may have had the infection for many years without knowing about it
- a partner may have been infected years earlier and, be unaware of it.

#### Why might I be tested for HPV?

##### HPV testing in women with borderline or mild dyskaryosis

If a woman's screening result shows mild abnormalities (called borderline or mild

dyskaryosis) an HPV test will be carried out on her sample. Women with borderline or mild dyskaryosis have only a 15–20% chance of having an abnormality significant enough to need treatment.

The HPV test is important because the presence or absence of HPV indicates which women might need treatment. If HPV is found in her sample the woman will be invited to go for colposcopy. Colposcopy involves looking closely at the cervix to see whether any treatment is needed. If it is, she will normally be seen in an Outpatients Clinic, which means that there is no need to stay in hospital overnight.

##### HPV testing in women who have received treatment for CIN

If colposcopy reveals CIN and the woman is treated for it, she will be screened once again around six months after her treatment. If the result is normal, borderline or mild the sample will be tested for HPV. If HPV is not found she will not need to be screened for another three years.

If HPV is found, or if the screening result shows moderate or worse dyskaryosis, the woman will be invited for colposcopy again. She will then be treated or (if treatment is not needed) monitored in line with the national guidelines covering women who have had colposcopy.

##### How is the HPV test done?

The test is done using the sample of cells taken during the screening test, so there is no need to be screened again.

##### Where can I find more information?

If you would like more information about HPV testing, or about anything else mentioned in this factsheet, talk to your practice nurse or visit the NHS Cancer Screening Programmes website at [www.cancerscreening.nhs.uk](http://www.cancerscreening.nhs.uk).





# NHS Cervical Screening Programme

## Frequently asked questions

### Human Papilloma Virus

#### What is Human Papilloma Virus (HPV)?

It's a small virus comprising around 100 types. Some of these types cause non-genital lesions such as common warts; others cause genital lesions, including genital warts. The type that causes genital warts (type 6) is not linked with cervical cancer but around 20 or so types are – particularly types 16 and 18. It is these 'high-risk' types that we are testing for. The virus replicates within the epithelium or mucosa of the cervix and sheds in exfoliated cells which can be detected in cytology samples.

#### Why test for HPV?

It is now very clear that when a woman has borderline and mild abnormalities only the high-risk HPV positive lesions are likely to have CIN. This means that high-risk HPV negative women need not be referred to colposcopy. It also means that high-risk HPV positive women should be referred to colposcopy without the need for repeat cytology follow up, which simply delays the final diagnosis.

In addition, treated women who have normal, borderline or mild cytology six months after their treatment and who also test negative for high-risk HPV are at very low risk of cervical cancer and need not be screened again for three years.

#### How do we test for high-risk HPV?

The cervical sample that was used in cytology is re-used in HPV testing. This means that when borderline or mild dyskaryosis is reported, or a normal, borderline or mild result is reported following treatment, the material left after the cytology slides have been prepared is used to test for high-risk HPV. The remaining cervical cells are processed to allow any viral DNA in the cells to be detected.

#### How is HPV acquired?

It is generally accepted that cervical HPV infection is acquired through sexual contact. The epidemiology of cervical cancer has for many years indicated increased risk in women with multiple partners and early onset of sexual activity. This suggests that a sexually transmitted agent is involved in cervical carcinogenesis.

It is common for women to state that their current partner has been their only sexual partner, and for their partner to say the same. Theoretically, if two virgins form a faithful sexual relationship there should be no opportunity to acquire HPV. Yet we know that some women in relationships of this type do test HPV positive. HPV infections can persist for many years and it is not possible to be sure when the infection occurred or what its true source is. Certainly the HPV types most often associated with cervical cancer are usually symptomless in both partners.

This can be a difficult area, but a gentle explanation of the facts as we understand them usually suffices. If a woman who has had only one sexual partner acquires cervical HPV do not be tempted to suggest that this indicates infidelity.

#### How long does HPV infection last?

HPV infection of the cervix usually occurs earlier in the sexual lives of women. We know this because high-risk HPV positive rates are about 50% in women around the age of 20. In most women the infection clears, usually within a year, and protective antibodies may develop to prevent future infection by the same HPV type. However, this does not always happen and it is not uncommon to acquire new HPV infections of a different type. In some women (probably 20–30%) the infection persists and may do so for years. The longer the infection

persists the greater the risk of subsequent abnormality.

### **How can high-risk HPV cause cancer?**

HPV contains several genes that can disturb the mechanisms regulating normal cell division, which then becomes uncontrolled. It is thought that HPV alone may not be sufficient to cause cancer and that other factors, such as smoking, may play a part.

### **Can HPV infection be treated?**

At present there is no effective treatment for HPV infection but, as stated, the immune system clears most infections.

### **Can HPV infection be prevented?**

Research suggests that the two vaccines developed by international pharmaceutical companies are very effective at preventing infection with the two virus types most commonly linked with cervical cancer. But these types are responsible for only around 75% of cases. A national HPV immunisation programme is currently under way to routinely vaccinate girls aged 12–13 years, together with a two year catch up programme for girls up to 18 years. As vaccines are ineffective in women who are already infected, screening will still be needed in the future.

## APPENDIX 5 Guidance notes and sample standard operating procedures for the packaging and transport of HPV vials and tubes

### (a) Guidance notes on the transport of biological materials

The Scottish HPV Reference Library has produced detailed guidance on the transport of biological materials, accompanied by a list of useful internet resources. This guidance is being made available separately via [the NHSCSP intranet site](#).

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## (b) Choosing a courier and suitable transport boxes

Most laboratories will already have local contracts with couriers for the routine transportation of samples. The choice of courier for transporting cytology samples to other locations will continue to be made locally, allowing laboratories to use couriers they are already familiar with. However, it is important to establish whether or not the courier is able to offer a comprehensive Biological Substances transport service. To aid couriers when initial arrangements for shipping are being made it is essential that they are provided with the following information

1. a full description of the goods to be transported
2. the relevant UN number (UN3373)
3. the correct shipping name (ie the consignee's full name).

If laboratories are in any doubt about a courier's experience in transporting dangerous goods an alternative must be sought.

Goods subject to the *UN3373 Biological Substance Category B* transport regulation have to conform to a corresponding packing instruction. All LBC samples transported to Virology must be packed in accordance with Packing Instruction 650 (PI650). This requires the LBC sample (the primary receptacle) to be packed in secondary packaging and a rigid outer packaging. In this case the rigid outer packaging will be the transport box.

For further information, see the detailed guidance on the transport of biological materials available on [the NHSCSP intranet site](#).

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## (c) Transporting ThinPrep samples<sup>‡</sup>

**NB ThinPrep samples are transported at ambient temperature.**

1. Ensure that each vial lid is tightly closed.
2. Seal the vial by wrapping Parafilm securely around the lid.
3. Place each vial in a specimen bag and seal it.
4. Put the specimen bags into the large PE bag (containing the absorbent pads) and place the bag in the transport box.
5. Seal the top of the PE bag, ensuring that the corners are folded shut and held together by a grip.
6. Place a contents list into the top of the box.
7. Close and lock the transport case, ensuring that the destination details are clearly displayed on the side of the case.

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<sup>‡</sup> Transport guidance for other suitable platforms will be posted on the intranet site once they are formally approved for use in the NHSCSP.

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## (d) Transporting SurePath samples

NB For HPV testing with Qiagen Hybrid Capture 2, SurePath tubes must be topped up to approximately 2.8mls with SurePath preservative fluid immediately after cytology processing, in accordance with Qiagen's instructions. **If the specimen appears to contain less than 1ml of fluid when received at the HPV testing laboratory, it is possible that SurePath preservative fluid was not added post-cytology, in which case the specimen will not be suitable for high-risk HPV DNA testing.**

Residual volume from SurePath pots **should not** be sent to HPV testing laboratories.

**NB SurePath samples are transported at ambient temperature.**

1. Replace the caps of each tube with one of the screw-top lids provided by Medical Solutions. Ensure that each lid is tightly secured.
2. Seal the tubes by wrapping Parafilm securely around the lid of each one.
3. Place the sealed tubes in the storage rack and place the rack in the PE bag (containing the absorbent pads).
4. Place the PE bag in the transport box, balancing the rack on the inner rim.
5. Seal the top of the PE bag, ensuring that the corners are folded down and held together by a grip.
6. Place a contents list in the top of the box.
7. Close and lock the transport case, ensuring that the destination details are clearly displayed on its side.

Test tube racks should be no longer than 265mm and able to accommodate test tubes that are 16mm in diameter. In order to fit into the transport case the dimensions of the rack should be roughly 246x104x70mm.

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## APPENDIX 6 Training requirements for HPV testing for triage and test of cure

These training requirements for HPV testing relate to the following staff

1. cytology laboratory staff dealing with clinical aspects of HPV triage and test of cure
2. laboratory staff undertaking HPV testing
3. colposcopists receiving HPV referrals
4. primary care sample takers.

### 1. Training for cytology laboratory staff

The recommended duration of the training is one half day. It should be undertaken by consultants, ABMSPs/BMS consultants, BMSs and all screening staff. At least one consultant and one laboratory manager from each cytology laboratory site must attend. The lead consultant must subsequently confirm in writing that the course content has been cascaded to all pathologists, BMSs and cytology screeners.

#### *Indicative course content*

- brief review of molecular and epidemiological science of HPV
- HPV testing protocol (triage and test of cure)
- results of Sentinel Sites project
- quality assurance – expected changes in KC61 data
- HPV workflow through the cytology laboratory
- practical dilemmas (eg in the context of MDT)
- 'off label' HPV testing.

Training Schools may wish to link this with a half-day update on reporting borderline change, with a microscopy session.

### 2. Training for laboratory staff undertaking HPV testing

It is anticipated that training will be provided in the first instance by suppliers of HPV test technology and thereafter as part of update training.

Suppliers must submit their training protocol for approval by QARCs. Among the criteria for approval are that

- training will be provided on site
- all staff undertaking testing must complete the training
- certification of completed training must be provided.

If a laboratory decides to adopt more than one HPV test method, staff must be trained to this level of competence in each of the tests used.

### *Quality assurance*

To provide robust assurance of competence and reproducibility of results, each laboratory and staff member performing HPV testing should test a validation panel (consisting of up to 88 samples, including replicates) in two different runs. The panels will be produced by the Scottish HPV Reference Laboratory (which is also the UK's reference laboratory), to which results will be returned for analysis. If the anticipated results are obtained in more than 87% of samples (in line with non-inferiority guidelines) this will be taken as evidence of proficiency. Laboratories should also re-test every 100<sup>th</sup> sample to check for day-to-day reproducibility; this will be kept under review and may be refined in the light of experience.

The Reference Laboratory's assessment of proficiency will be an important addition to the NHSCSP's QA processes and their determination of a laboratory's overall readiness to go live with HPV testing.

The Reference Laboratory will also provide each HPV laboratory in its first year of operation with sufficient validated internal quality control material to be able to run a known positive and known negative sample (in addition to kit controls) once per week. Thereafter HPV testing laboratories should be able to produce their own internal quality control material.

## **3. Training for colposcopists**

All colposcopists who will receive HPV referrals are expected to attend training and undertake relevant study. While the final course programme will be agreed by the NHSCSP's Colposcopy Quality Assurance Group and the British Society for Colposcopy and Cervical Pathology, an indication of possible course content appears below

- the science and epidemiology of HPV
- the HPV triage and test of cure protocol for England
- the implications for recall and failsafe
- evidence base for HPV triage and test of cure protocol, including data from the Sentinel Sites study
- the role of HPV testing in the management of difficult clinical scenarios.

## **4. Training for primary care sample takers**

Training for primary care sample takers will be based on the NHSCSP information pack at Appendix 4. It may be delivered in person (via courses and/or seminars), in the form of posted material, or online. On completion of their training, all sample takers must sign to confirm they have understood the changes to the programme and will be able to counsel women appropriately.



## APPENDIX 7 Women with negative satisfactory colposcopy can be safely returned to routine recall after triage and test of cure: a BSCCP/NHS colposcopy alert

**John Tidy, Patrick Walker and Henry Kitchener on behalf of the NHSCSP Sentinel Sites HPV Special Interest Group**

The introduction of HPV triage and 'Test of Cure' [TOC] will lead to significant changes to the cervical screening programme.

The advantages of these new strategies are:-

- women with minor cytological abnormalities who are HPV+ve benefit from rapid referral to colposcopy to identify high grade CIN
- rapid return of women to routine cervical recall when there is no evidence of CIN on colposcopy
- avoidance of referral to colposcopy of women with low grade cytological abnormalities who are negative for high-risk HPVs
- avoidance of unnecessary community based follow up of women with minor cytological abnormalities (borderline nuclear changes and mild dyskaryosis)
- rapid return to routine recall for women successfully treated for CIN.

To maximise these benefits it is necessary to introduce new pathways of care for women referred to colposcopy as part of HPV triage and 'Test of Cure'; who have negative and satisfactory colposcopy. This paper provides an evidence base for these new pathways.

There are two key issues:-

1. the negative predictive value of negative colposcopy at triage to exclude underlying high-grade CIN, in terms of the risk of such women developing high grade CIN during the next 3 years, i.e. the next screening round.
2. The negative predictive value of normal colposcopy after treatment, when follow up cytology is low grade and/or HPV+ve, in terms of the risk of such women developing high grade CIN during the next 3 years, i.e. the next screening round.

The evidence required to answer these questions comes from the research literature as well as from prospective NHSCSP studies designed to address these issues. The evidence to support the negative predictive value of colposcopy in the presence of low grade cytological abnormality was reviewed in NHSCSP No 20. It led to a recommendation that women should have repeat cytology in six months. This was based on a cumulative risk of CIN3 of 3-10% reported from retrospective studies <sup>1-3</sup>. The cross sectional negative predictive value for colposcopy to exclude high-grade CIN, when colposcopy is described as normal, has been reported as 98-99% <sup>4-6</sup>. More recent data are, however, more reassuring. A follow-up study of a cohort of women who had a negative colposcopic examination following referral for HPV positive low grade cytology, has recently been completed <sup>7</sup>. This showed that among 956 such women the cumulative rate of CIN2 or worse after a mean follow-up of 27 months was 4.4%, CIN3 recurred in 2.4%, with no cancers found. This compares with a normal prevalence of CIN2+ of around 1.2% in the screened population, and is considered sufficiently low to allow return to routine recall <sup>8</sup>.

What is the risk for a woman, who has had a normal colposcopic examination following treatment for CIN, but is high risk HPV positive, of developing high grade CIN during the next 3 years?

Outcome data at first follow-up of women who were part of the TOC sentinel study are available. 406 women were treated for CIN [CIN1 36, CIN2 222, CIN3 158]. 25.7% failed TOC at 6 months after treatment; 15.6% had abnormal cytology and 10.1% had normal cytology but were positive for high-risk HPV. In addition 3203 women who had previously been treated for CIN were part of the non HPV triage TOC study [CIN1 319, CIN2 941, CIN3 1939, Cancer 4]. 18.3% failed TOC at 6 months after treatment; 6.2% had abnormal cytology and 12.2% had normal cytology but were positive for high-risk HPV. Overall the rate for CIN2+ was 6.9%; for women with abnormal cytology the rate was 13.3%, and for women positive for high-risk HPV with normal cytology the rate was 2.7%. The positive predictive value to detect CIN3 or worse was 8.5% for abnormal cytology and 0.4% for women with negative cytology and a positive HPV test.

Longer term follow-up data are now available from a prospective HPV test of cure study which originally reported in 2008<sup>9</sup>. 917 women seen 6 months following treatment for CIN had been treated by excisional methods [CIN1 217, CIN2 326, CIN3 365, HGCGIN 6]. 25.3% [173 women] failed TOC at 6 months after treatment, 10.7% had abnormal cytology and 14.6% had normal cytology but were positive for high-risk HPV. The overall proportion of failed treatment was 4.6%; 9.2% in those with abnormal cytology and 2.6% in those with negative cytology and HPV positive. The positive predictive value to detect CIN2 or worse was 11.8% for abnormal cytology and 2.6% for women with negative cytology and a positive HPV test. Amongst 302 of 744 women who were both cytology and high-risk HPV negative and had colposcopy CIN1 was detected in eight and CIN2 in one.

The data for this cohort has recently been updated with 617 (67.3%), 445 (48.5%) and 159 (17.3%%) being followed up to 36 months, 60 months and 84 months respectively. At the first follow-up visit at 6 months 11 (1.2%) cases of CIN2+ were detected. By 3 years an additional 18 CIN2+ (18/617 2.9%), by 5 years six CIN2+ (6/445 1.3%) and by 7 years a further three cases of CIN2+ (3/159 1.9%) had been detected. This demonstrates clearly that the TOC protocol which treats detected abnormalities at 6 months, discharges to 3 yearly recall women who were cytology -ve/HPV -ve as well as those with abnormal results but negative colposcopy at 6 months, is a safe policy.

Conclusion. Women either triaged following low grade cytology or referred following failed test of cure, who have negative satisfactory colposcopy, can be safely discharged to 3 yearly recall. This strategy will avoid the accumulation of women with indeterminate results in a process of prolonged follow-up.

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## APPENDIX 8 Department of Health publications orderline

Copies of the *HPV Triage and Test of Cure Information Pack for Primary Care* and the leaflet *HPV Testing Information for Women* are available from the Department of Health publication orderline quoting HPV FOLDER or HPV LFTWOMEN.

Telephone: 0300 123 1002

Department of Health Publications  
PO Box 777  
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