HPV testing in the follow-up of women post colposcopy treatment
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**Background**

CervicalCheck - The National Cervical Screening Programme, which is part of the National Cancer Screening Service, has been in operation for over three years. The programme provides free smear tests to women aged 25-60 years at regular intervals. The National Cancer Screening Service is responsible for the governance and management of colposcopy services as part of CervicalCheck. As part of the programme, colposcopy services are delivered through a multidisciplinary team approach and provide the facilities for diagnosis, treatment and follow-up of women with an abnormal smear test result. The NCSS has made a significant investment in the development of colposcopy services at 15 locations nationwide. Testing for the human papillomavirus (HPV) will now be introduced for women post colposcopy treatment.

**Treatment of CIN and risk of recurrence**

Cervical screening programmes aim to reduce the incidence and mortality rates of cervical cancer through the detection and treatment of pre-cancerous cervical abnormalities\(^{(1)}\). While treatment reduces the risk of invasive cancer by over 90 per cent, treated women still have five times the risk of invasive cancer compared to women who have always had normal smear tests\(^{(2)}\). Special follow-up measures are required to try and further reduce these risks. Traditional protocols involve more intensive screening with annual cytology tests for up to 10 years, to facilitate the early detection of recurrence of high grade CIN\(^{(3)}\). This approach is not without its problems and probably represents over-treatment for as many as 90 per cent of those women. In addition, poor compliance over long periods of time risks default from surveillance\(^{(4)}\). Finally, anatomical changes post treatment can result in sampling issues for cytology testing, particularly where there is endocervical involvement or if there is post treatment cervical stenosis.

In recent years attention has focused on ways to define the risk of recurrence more accurately and to stratify follow-up protocols according to the risk\(^{(5)}\). The incorporation of testing for high risk HPV genotypes in addition to cytology is the strategy with the most potential to increase the efficiency and effectiveness of screening in this group of women\(^{(6)}\).

**The natural history of HPV infections**

It has become increasingly clear from emerging evidence that persistent infection with high risk subtypes of HPV is the key factor in the development of cervical cancer\(^{(7)}\). In excess of 130 genotypes of the virus have been identified to date, of which 15 have been classified as high risk, the most important of which are types 16, 18, 31, 45 and 52. Infection with HPV is very common - 80 per cent of women will become infected within 18 months of becoming sexually active. Most infections do not have symptoms and are short lived with the majority being cleared within a further 18 months. In a minority of women, the infection persists, leading to viral integration of the virus and the production of abnormal or dysplastic epithelium\(^{(8)}\).
HPV testing for women following treatment for CIN at colposcopy

Persistent infection with high risk HPV virus types following treatment has been proven to be associated with an increased risk of recurrent high grade CIN and these women require increased surveillance. The absence of HPV infection has been shown to be a valuable marker of a low risk of recurrent disease. As a result of these studies, HPV testing is being introduced in Ireland in 2012 as an adjunct to cytology in the follow-up of women who have been treated / received treatment at colposcopy.

CervicalCheck summary for HPV testing post treatment

All women should have a smear test and a HPV test at 6 months post treatment for CIN in colposcopy (includes conisation / LLETZ, ablative treatments and hysterectomy).

- HPV testing should not occur before 6 months post treatment.
- Cytology and HPV test will be taken at colposcopy (smear) clinic.

Repeat smear test and HPV test one year after the first - 18 months post treatment in colposcopy.

- Cytology and HPV test will be taken at colposcopy (smear) clinic.
- Women who repeatedly test negative for high risk HPV and who do not demonstrate LSIL or more severe cytological abnormality results at this point will be discharged from colposcopy with follow-up to routine call, re-call - either 3 or 5 year call depending on age.

Any woman positive for high risk HPV or cytology ‘LSIL+’ (at either 6 or 18 months) will need to undergo further colposcopy with repeat treatment if necessary.

- Women who do not need repeat treatment will require ongoing surveillance for 10 years most of which will be in primary care.

The CervicalCheck algorithm for HPV testing post treatment at colposcopy is presented in figure 1. CervicalCheck provides HPV tests for women post treatment at colposcopy, one to be taken at 6 months post treatment and the second to be taken at 18 months post treatment. Tests should be taken as a single sample, in a single bottle and forwarded to the CervicalCheck contracted laboratory with a single ‘Cervical Cytology & HPV form’ (Appendix 2). The results will be received in the colposcopy service with a single management recommendation.
Special circumstances

Women who have treatment for adenocarcinoma in situ or microinvasive cancer of the cervix (stage 1a1-stage 1a2) need extra special attention. The histology should be discussed at a multidisciplinary CPC/MDT meeting to ensure that the excision is complete before planning follow up. These women can avail of a combined HPV and cytology test at six and eighteen months at colposcopy as described above for women with CIN but these women may still require annual cytology for ten years at the discretion of the clinicians.

Suggested management of ‘out of programme’ HPV tests

Colposcopy services will from time to time choose to perform HPV tests for other indications. The CervicalCheck programme does not currently accept these tests. Where these tests are performed, it will be necessary to take two samples. One sample should be attached to a ‘Cytology only’ form and forwarded to the appropriate CervicalCheck contracted laboratory as normal. The second sample should be forwarded to the laboratory that the hospital has an agreement with for HPV testing. Please ensure that the ‘Cytology only’ form is used for the sample forwarded to the CervicalCheck cytology laboratory.

In these instances the CervicalCheck procedure should be recorded in the colposcopy computerised management system as “Smear” and not “Smear and HPV” to enable the CervicalCheck CSR to be updated accordingly. The performance of a separate non CervicalCheck HPV test should be captured separately either on the patient management details page of the Compuscope system or the procedure page of the Mediscan system.
Figure 1
HPV testing at colposcopy services - suggested management of women post treatment

Women following treatment at colposcopy

First review 6 months Cytology and HPV

- Cytology negative or ASCUS and HPV high risk Negative
  - Second review 18 months cytology and HPV
    - Cytology negative or ASCUS and HPV high risk negative
      - Discharge to routine screening
    - Cytology LSIL + or HPV high risk positive
      - Repeat colposcopy with biopsy if abnormal
        - Repeat treatment required?
          - Yes
            - Repeat treatment required
          - No
            - Cytology LSIL + or HPV high risk positive
              - Repeat treatment required
              - Cytological surveillance including annual smear tests for 10 years

**System changes**

The computer systems operated at colposcopy services have been adapted to enable the required changes to the follow-up schedule.

The following facilities have been made available to staff at colposcopy services:

<table>
<thead>
<tr>
<th>Facility</th>
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<tbody>
<tr>
<td>The ability to schedule a specific ‘Cytology and HPV’ test appointment.</td>
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<tr>
<td>The ability to generate a request form for a ‘Cytology and HPV test’, if appropriate.</td>
</tr>
<tr>
<td>A default request when the appointment is previously defined as ‘Smear and HPV’.</td>
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<tr>
<td>The ability to manually select where the appointment is defined as ‘Smear only’ but where a “Smear and HPV” test is required.</td>
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<tr>
<td>The ability to print out request form before the test is performed as a signal to the smeartaker to discuss HPV testing.</td>
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<tr>
<td>The ability to input into the computer that a HPV test has been performed in addition to the smear test.</td>
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<tr>
<td>Outputs should be changed to include reference to the HPV test.</td>
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<tr>
<td>Failsafe processes need to include the HPV test.</td>
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<tr>
<td>The ability to input the HPV test results into the computer and to discriminate between tests in terms of range of subtypes tested.</td>
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<tr>
<td>The performance of a HPV test should be included in the procedure code that is transferred to the Cervical Screening Register (CSR).</td>
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</table>

It should be noted that the following specific information in the ‘relevant clinical details’ section of the ‘Cervical Cytology & HPV Form’ must be included to ensure smooth processing of samples:

- ‘HPV’ should be clearly marked as ‘yes’.
- ‘Post Treatment Test’ should clearly highlight whether this is HPV test number 1 or 2.

The failure to complete these fields on the ‘Cervical Cytology & HPV Form’ may lead to a delay and possible non-processing of the sample for HPV test.
Women who have been treated should have a smear test and HPV appointment made. 

On arrival, the ‘HPV planned’ and ‘post treatment test number’ boxes should be checked and the Cytology and HPV form printed. 

The woman is given the ‘About your combined smear test and HPV test’ leaflet / information sheet. 

Ensure information on HPV and test number is included before sending sample to the laboratory in the usual way. 

The smearaker records the test in the computer by ticking both the ‘smear’ and ‘HPV’ boxes. 

The smearaker discusses the new test with the woman and if she is agreeable performs the test. 

The smear test and HPV test should be listed separately in the daily clinic specimen checklist. 

The result of each component of the test will be issued simultaneously with a single management recommendation. 

The clinic staff check that both components are complete and record receipt of the result. 

Result are sent to the woman as well as her GP. 

Letters and summary are generated including appropriate follow up recommendation. 

The results are then entered into the computer system and the appropriate plan selected.
**More detailed information about the HPV test**

Most established HPV tests report on a group of HPV types (high risk or low risk) and report either the presence or absence of these types. These tests have been responsible for generating most of the clinical research information about HPV testing to date\(^9\). The major benefit of these tests is the improved sensitivity over cervical cytology alone. A potential drawback however is reduced specificity because of the relatively high prevalence of HPV infections in women, most of which are self-limiting and not clinically significant.

The test which the CervicalCheck programme laboratories will use in the initial stages of this initiative is the Digene Hybrid Capture (HC2) test which determines the presence or absence of the following 13 types (HPV 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68). However, this area of biomedical research is rapidly evolving and as new tests continue to be developed, it is entirely possible that a different test will be used in the future.

**Summary of research findings on which this protocol is based**

A multicentre study of the natural history and clearance of HPV after treatment of precancerous lesions has confirmed clearance rates of 90 per cent following LLETZ and 80 per cent following ablative treatment after a follow-up period of two years\(^10\) or clearance of HR-HPV DNA has been proven to be an independent risk factor for treatment failure or success. The addition of a HPV test improves the sensitivity of a post-treatment test allowing the detection of early treatment failures even in the presence of normal cytology\(^11\). The negative predictive value of HPV testing is likely to yield the most benefits allowing reduction in unnecessary testing for many women\(^12\). In a study which examined the long term follow-up of 11,085 women in the multicentre HART study in the UK\(^13\), of 9247 women with both cytology and HPV negative results at the baseline only 9 (0.2%) had CIN2+ identified during the course of the subsequent five years. Of the 247 women who were HPV negative and who had an ASCUS or inadequate smear at baseline only six (2.4%) had CIN2+ identified during the subsequent five years. Looking at this data another way, 97.6 per cent of women with ASCUS who were negative for HPV did not develop CIN2+ in the subsequent five years. Unnecessary colposcopy can therefore be avoided in this group of women.
Appendix 1

Information for women

About your combined smear test and HPV test

Why are you being offered a combination smear and HPV test?

This new test is being offered to women who have had a treatment at colposcopy following a CervicalCheck smear test and an abnormal smear test result. It can help reduce the need for annual smear tests for 10 years after a treatment at colposcopy.

What is HPV?

HPV is the human papillomavirus. HPV is a very common infection of the cervix (the neck of the womb). Most women get HPV at some time in their lives. In most cases it does not need treatment and the body will clear a HPV infection on its own.

How do women get HPV?

In most cases, HPV is passed on by direct skin to skin contact during vaginal, anal, or oral sex with someone who has been infected with HPV. Most women who are sexually active will have HPV at some time. In most cases, the virus does not cause any problems and disappears naturally over time. The virus has no symptoms so women can have it for many years without knowing about it.

How is HPV treated?

There is no cure for HPV. In most cases, the body will clear a HPV infection on its own. When the HPV clears, the cervical cells go back to normal. However, even though there is no cure for the virus, its effects, such as abnormal cells on the cervix (neck of the womb), can be treated. If the HPV leads to abnormal cells on your cervix, they will be treated or removed at the colposcopy clinic. This treatment is usually very successful.

How is the combination smear test and HPV test done?

Six months after your treatment at colposcopy you will have a smear test. The sample taken at this smear test is tested for HPV. The sample is examined in a laboratory and you will be sent your result in the post.
What happens if HPV is found?
If HPV is found or if the test shows abnormal cells, you will be invited for a colposcopy again to check for any persisting abnormality. If you need more treatment at colposcopy, you will start the post treatment process again with two combination HPV and smear tests – one at six months after your treatment and another a year after that.

If you do not need more treatment, you will still need to have a smear test every year for 10 years to monitor the situation, as you could still develop changes in your cervix. It is important that you go for your smear test when invited so that any abnormality can be detected.

What happens if no HPV is found?
If your result is normal and no HPV or abnormal cells are found, you will be invited for another combination HPV and smear test at the colposcopy service in one year. If the result of the second test a year later is again normal, with no HPV and no abnormal cells, you can return to routine screening by smear test every three or five years, depending on your age.

Where can I find more information about HPV?
You can talk to your doctor or colposcopy nurse.

The CervicalCheck website (www.cervicalcheck.ie)
Appendix 2

Sample Cervical Cytology and HPV Form
References


The National Cancer Screening Service is part of the Health Service Executive National Cancer Control Programme. It encompasses BreastCheck – The National Breast Screening Programme and CervicalCheck – The National Cervical Screening Programme.

Freephone information
1800 45 45 55

Website address
www.cervicalcheck.ie