The National Cancer Screening Service is part of the Health Service Executive. It encompasses BreastCheck – The National Breast Screening Programme and CervicalCheck – The National Cervical Screening Programme, BowelScreen – The National Bowel Screening Programme and Diabetic RetinaScreen – The National Diabetic Retinal Screening Programme.
Chapter 5
Quality assurance in HPV testing

5.1 Introduction

5.2 Quality requirements and standards
   5.2.1 Organisational requirements
   5.2.2 Laboratory facilities
   5.2.3 Staff qualifications
   5.2.4 Specimen reception
   5.2.5 Data entry and notification to CervicalCheck
   5.2.6 Sample processing
   5.2.7 Proficiency and competency of staff
   5.2.8 Results management
   5.2.9 Storage and archiving
   5.2.10 Quality assurance and continuous improvement

5.3 References
5.1 Introduction

The role of persisting high risk human papilloma virus (HR-HPV) infection among women with cervical intraepithelial neoplasia (CIN) and cervical cancer is now clearly established.

HPV testing post colposcopy treatment was introduced into the cervical screening programme in 2012. The reported negative predictive value of HR-HPV testing for CIN is over 99 per cent, therefore women who are negative for HR-HPV post-treatment are at very low risk of residual disease and may be discharged to routine re-call. By employing HPV testing post colposcopy treatment, approximately 80 per cent of treated women avoid having to undergo annual smear tests. HPV testing may be employed in other scenarios in due course. These include ASCUS triage which will allow women who receive a cytology result of ASCUS but are HPV negative and therefore at low risk to be returned to routine re-call. Those who are ASCUS on cytology and HPV positive can be followed-up at colposcopy services as appropriate. HPV testing may also be employed for the management of difficult cases in colposcopy.

HPV testing for CervicalCheck is carried out on the residual fluid remaining in the Thinprep® vial post-processing for cytology screening. As both tests are carried out on the same sample, the programme requires the cytology laboratory to inform it when a HPV test has been ordered or authorised. The same laboratory accession number is required for a combined cytology and HPV sample. For this reason, many of the requirements below are also outlined in Chapter 4.

HPV testing may be carried out in the cytology laboratory, a microbiological lab or a dedicated molecular testing laboratory. Regardless of the location of the testing environment, there are a number of quality requirements and standards that must be in place to ensure accurate and reliable results. The requirements are essential elements in the organisation, management and interface of a laboratory operating within a cervical screening programme. The standards are the metrics for specific elements of the performance of a laboratory. The statement of each standard is accompanied by both an achievable and a minimum target.

The quality requirements and standards for laboratories providing HPV testing services to CervicalCheck are set with regard to the evolution of standards and guidelines in response to technological developments and research outcomes in other cervical screening programmes, with particular reference to revisions in the NHS ‘CSP Publication No. 1’ (revised 2012)¹ and the NHS ‘HPV Triage and Test of Cure: Implementation Guidance’² document.

Compliance with the requirements and standards is measured and monitored by:

- Quality metrics reports by laboratories
- Analysis of data provided to the Cervical Screening Register (CSR) by cytopathology, colposcopy and histology services providers
- Quality assurance site visits to laboratory providers
- Monitoring and review of operational activity and performance.
5.2 Quality requirements and standards

Ensuring quality assurance in service delivery comprises compliance with both quality requirements and quality standards.

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<th>Quality requirements</th>
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<td>are stated as a description. There are no targets associated with a requirement as service providers must fulfil the requirement.</td>
<td>are stated as a description of an activity with a measurable level of performance, with an associated target for achievement. The standards are designed to be measurable i.e. quantitative with criteria that are valid, reliable and feasible.</td>
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Several of the quality requirements and standards set out below may be simultaneously fulfilled if HPV testing is carried out by a cytopathology laboratory providing services to the screening programme.

5.2.1 Organisational requirements

**Accreditation**

The laboratory will have and maintain accreditation to ISO15189 standard or equivalent, certified and documented by an approved accreditation body. The scope of the laboratory accreditation must include HPV testing.

External accreditation at least once every 2 years.

**Note:** Laboratory accreditation covers facilities, staff qualifications, training and competencies, equipment, laboratory information systems, and quality management systems.

**Data protection**

The storage, access and transfer of women's personal and health information shall be compliant with the Data Protection Act 1988 and the Data Protection (Amendment Act) 2003 and any future revisions or amendments of the Act as well as the EU Directive 95/46/EC - The Data Protection Directive.

**Health and safety compliance**

The laboratory shall be compliant with all national legal and statutory health and safety requirements. The Clinical and Laboratory Standards Institute (CLSI) document ‘MM3-A2-Molecular Diagnostics Methods for Infectious Diseases; Approved Guideline-Second Edition’ is the reference document recommended.
Quality management system (QMS)
The laboratory shall have a quality management system (QMS) in place as required by their accreditation standard. The laboratory shall have a designated person responsible for quality management who will liaise with CervicalCheck to resolve any quality issues that may arise.

Any complaints in relation to the service shall be notified to the NCSS.

Security of electronic data exchange with programme
A Virtual Private Network (VPN) shall be installed between the laboratory and the programme operations office for the secure exchange of electronic data.

Laboratory information management system (LIMS)
A computerised laboratory information management system (LIMS) will be installed and be in operation in the laboratory.

The LIMS will be in a secure facility with adequate backup arrangements, on- and off-site. Access to the LIMS will be by privilege-level access control. The LIMS will be capable of generating periodic quality metrics and audit returns to CervicalCheck.

Data capture
The LIMS will be capable of recording the data required by CervicalCheck (Cervical Screening Register information system data entry standards demographic details) from the sample and Cervical Cytology Form or Cervical Cytology and HPV Form.

Format and timing of electronic data exchange with the programme
The LIMS will be capable of extracting and transferring required data to the programme in the required format as per CervicalCheck specifications (notification and result files). The laboratory will also receive information from the programme in specified formats and transfer it to its information systems (error and history/eligibility files).

The laboratory will have in place the capability to exchange electronic communications between staff members and programme staff through secure protocols (e.g., secure email).

Reporting
The LIMS will be capable of recording test results including combined cytology and HPV management recommendations. The LIMS will be capable of recording the identity of the person authorising the HPV report.
Capability and format for electronic orders and results

It is desirable that laboratories are capable of receiving orders electronically and issuing results electronically to and from ordering doctors or clinics, according to a specified messaging standard. Electronic laboratory order format is HL-7 based and conforms to the Laboratory order message specifications of the Health Information and Quality Authority (HIQA) current GP Messaging Standard. HL-7 based orders and results use Healthlink’s Message Broker System. The physical form for electronic orders includes a barcode, which laboratories shall be able to scan and extract the included details for automatic import into their data entry system.

In addition the laboratory information system (LIMS) should:

• Link multiple test results for the same patient
• Provide easy access to details of previous cervical cytology and histology of the patient
• Provide a mechanism for ascertaining and recording clinical outcome after cytology tests, including colposcopy findings, biopsies and reasons for biopsies not being taken
• Provide the data necessary for evaluation of the cervical screening programme.

Changes to service capacity, capability or conformance to quality assurance standards

Any changes that impact on or could have an impact on any aspect of laboratory services, including laboratory accreditation status, processes, system procedures, analysis, and reporting will be agreed with CervicalCheck. Any changes will be advised in advance in writing to CervicalCheck.

Other laboratories

Laboratory/ies will make relevant clinical information and follow-up data available to other laboratories providing services to CervicalCheck.

Health agencies and authorities

Laboratories engaged by CervicalCheck will comply with all requests for data or reports by Irish health agencies and authorities, including the Department of Health and the National Cancer Registry Ireland (NCRI).
5.2.2 Laboratory facilities

HPV testing services will be provided in a dedicated laboratory area or facility. All areas will be clean, well lit and well ventilated. There will be appropriate storage facilities for flammable and toxic chemicals as required by national legal and statutory health and safety requirements.

5.2.3 Staff qualifications

Scientific, medical and non-medical staff will be qualified for the positions they hold according to national requirements to practice.

The laboratory carrying out HPV testing will be led by, or have access to a medically qualified consultant who works in that discipline on a regular basis. This is to facilitate high-quality testing and support the effective management of more challenging cases.

There will be a lead medical scientist or manager who is responsible for the day-to-day management of the department and has responsibility for supervision of non-medical staff.

Roles and responsibilities will be defined and should be incorporated into the laboratory quality manual.

5.2.4 Specimen reception

Standard operating procedures (SOPs) will be in place for handling CervicalCheck samples. Laboratories will accept orders via postal delivery and via electronic laboratory orders where applicable (followed by the receipt of the physical sample and form). For electronic orders the laboratory will be capable of extracting bar-coded information.

The laboratory will only accept programme samples from doctors or clinics that are notified to the laboratory by CervicalCheck. Only those samples accompanied by the programme’s Cervical Cytology Form\(^9\) or Cervical Cytology and HPV Form\(^10\) will be accepted. Only those samples indicating either signed consent or prior consent by the woman will be accepted.

All forms will be date-stamped upon receipt.

Sample vials will be matched to the accompanying forms prior to labelling. To ensure a robust ‘chain of custody’ cross-checking of a minimum of three and preferably four patient identifiers will be performed. If the testing procedure requires initial aliquoting from the LBC vial then a second person verification should be in place to ensure a robust ‘chain of custody’.

A discrepancy handling and resolution process will be in place to manage all discrepancies with CervicalCheck samples received. A CervicalCheck guidance document ‘Cervical smear samples laboratory – samples receipt. Discrepancy handling and resolution guidance’\(^{12}\) is available for laboratories contracted by the programme. Discrepancies with received samples will be recorded and the log will be made available to CervicalCheck. The format of the log will be approved by CervicalCheck.

Samples returned to ordering doctors or clinics will be traceable.

After verification of correct correlation of the sample vial with the corresponding form, and acceptance of the sample and form for processing, both will be labelled with a unique identification number (laboratory accession number).

The unique laboratory accession number for the sample must remain the same whether the sample is for cytology screening only, for HPV testing only, or for both cytology screening and HPV testing.
5.2.5 Data entry and notification to CervicalCheck

Data entry of the details recorded on the forms accompanying submitted sample vials will conform to CervicalCheck data capture requirements.

All relevant data recorded on the form by the smeartaker will be entered into the LIMS (refer to Cervical Cytology/Cervical Cytology + HPV/Cervical HPV Requests and Results).

Samples will be assigned to the correct clinically responsible doctor or clinic (Registered Smeartakers – Types and Identification).

**Access to received HPV test order forms**

Copies of all submitted HPV test order forms (HPV test only or combined cytology and HPV test orders), in electronic format and indexed by the laboratory accession number, shall be made available promptly to CervicalCheck.

100%, within 7 working days of acceptance.

**Standard 5-2**

**Notification of sample receipt to programme**

Samples, once accessioned, must be notified promptly by electronic means to CervicalCheck.

95% within 48 hours of receipt of sample. Min: 80% by 17:00 GMT next working day.

**Standard 5-3**

**Note:** A tracking system or log will be in place to verify that the number of electronic notifications sent to CervicalCheck on any given day equals the number of samples entered onto the LIMS that day. A weekly reconciliation of files sent and received will be in place between CervicalCheck and the laboratory.

**Programme ineligible samples**

Samples identified by CervicalCheck as ineligible for the screening programme will not be processed. Certain samples that are not to be processed may have to be reported. These include expired vials and samples that are not processed but a report is sent to both CervicalCheck and the requesting doctor. Ineligible samples may be required to be returned to the ordering doctor or clinic.
5.2.6 Sample processing

The HPV test used will be chosen from those considered acceptable for use within the CervicalCheck programme and agreed by contract.

Analysers will be installed by the manufacturer’s personnel. The installation will be in an appropriate environment to ensure accuracy and validity of results and to prevent contamination.

Periodic maintenance will be carried out by trained individuals as specified in the manufacturer’s user manual. A log of maintenance will be maintained.

The laboratory must verify that instrument, analyser, and reagent performance meets the published specifications. Appropriate personal protective equipment and handling techniques will be employed to prevent contamination of samples.

Reagents must be within expiry date. Reagents and samples will be stored according to specified storage conditions. Only those reagents or consumables specified by the manufacturer will be in use.

Processing of samples will be carried out according to instrument user manuals and assay specific package inserts.

All laboratories providing HPV testing will include positive and negative internal quality control (IQC) samples as well as all required kit controls in every run. The quality of the analytical runs may be monitored using additional quality assurance (QA) guidelines such as the Westgard rules\textsuperscript{15}.

**Quality requirement**

**Sample ‘chain of custody’**

Handling procedures will ensure a robust ‘chain of custody’ across all phases of the analysis, including specimen receipt, nucleic acid extraction, nucleic acid quantification, hybridisation/amplification, detection, documentation and storage. An audit trail will be in place for sample processing.

5.2.7 Proficiency and competency of staff

Laboratory staff implementing HR-HPV technology will have relevant experience in interpreting and troubleshooting molecular technologies. They will have appropriate training to include sample handling, analysis, quality control and health and safety.

**Quality requirement**

**Continuing education**

There will be protocols and practices in operation to demonstrate a system of both internal and external continuing education for scientific and medical staff reporting CervicalCheck cases.
5.2.8 Results management

For diagnostic purposes, results will be assessed in conjunction with the patient’s medical history, clinical examination, and other findings. There will be a documented system in operation to detect and correct significant clerical and analytical errors, and unusual laboratory results, in a timely manner.

**Quality requirement**

**Reporting HPV test results**

HPV result codes will be reported with the detail and the format specified by CervicalCheck. Generally, the details required include: HPV test methodology, HPV test result, subtypes tested and reference range.

**Quality requirement**

**Assignment of management recommendations**

All cytology results will take the HPV test result into consideration and have a management recommendation accompanying the cytology pattern as a P and R code combination according to ‘Cervical Cytology Management Recommendations Explanatory Guide’\(^\text{16}\) and ‘Cytology Terminology Table’\(^\text{17}\) as appropriate.

*Note:* Where a combined cytology screen and HPV test is carried out, the management recommendation will be assigned using Cytology and HPV Recommendations Table for follow-up of women post-treatment, or similar CervicalCheck publication for other HPV test scenarios.

**Quality requirement**

**Management recommendations with respect to screening history**

Management recommendation will be correct for each result with respect to the screening history of the woman.

The screening history of the woman provided by the smear-taker via the Cervical Cytology Form\(^\text{9}\) or Cervical Cytology and HPV Form\(^\text{10}\) and CervicalCheck from the CSR (where such history is available) must be referred to and taken into account during the results process. This will ensure the correct management recommendation is assigned.

CervicalCheck uses the management recommendation accompanying results to issue appropriate correspondence to a woman advising her of her next recommended step in the screening programme.

**Quality requirement**

**Check of result and recommendation**

An independent check of the case result and management code will be in place, prior to report authorisation, to minimise the risk of error.

**Quality requirement**

**Authorisation of results**

Every result will be appropriately authorised before release. Every report will be checked for inconsistencies before authorisation. Reports will identity the cytotecnologist or medical scientist and/or cytopathologist responsible for the conclusion and recommendation.
**Result codes notification to programme**

Results, once authorised and released, will be issued in the agreed summary format as soon as possible by electronic means to CervicalCheck.

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**Standard 5-4**

**Laboratory response time (turnaround time [TAT])**

Cytology results must be authorised, released and transmitted to CervicalCheck within the target turnaround time from sample validation by the programme.  

95% within 10 working days.

**Note:** If the target for turnaround time (TAT) cannot be achieved for any period exceeding three working days, CervicalCheck will be immediately informed and a plan to remove the delay must be provided within one week.

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**Adequacy of results reports**

The contents of the results report to ordering doctors and clinics must be in accordance with the guidelines outlined in Cervical cytology/Cervical Cytology + HPV/Cervical HPV Requests and Results.

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**Standard 5-5**

**Results reports to ordering doctors or clinics**

Results, once authorised and released, must be issued promptly to the ordering doctor or clinic.  

99% to be received within 5 working days.

**Note:** The issuing of results must take account of the time taken for delivery of printed paper results (post or courier) to meet the target for receipt by the ordering doctor or clinic.

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**Delivery of results reports to ordering doctors or clinics**

Results reports will be issued to the correct ordering doctor or clinic. Documented processes are required to ensure that results are sent to the correct doctor and to handle discrepancies between the number of samples received and the number of reports transmitted.

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**Results reports by electronic means**

It is desirable that all results reports in addition to paper format be issued to ordering doctors or clinics and CervicalCheck in full electronic format via a nominated telecommunications pathway. The electronic format for results is HL-7 based and conforms to the laboratory result message specifications of HIQA’s GP Messaging Standard.
5.2.9 Storage and archiving

The laboratory will ensure adequate administration and secure archiving and disposal of forms, samples, waste products and reports. Records will be stored to allow prompt retrieval if required.

Administration, archiving and disposal procedures will comply with accreditation standards and national legislation, including those relating to confidentiality and data security of personal health information.

**Quality requirement**

Access to materials

Laboratories are required to provide CervicalCheck access to materials including logs and records, on request.

5.2.10 Quality assurance and continuous improvement

**Quality requirement**

External quality assurance (EQA)

All laboratories providing HPV testing will participate, and show adequate performance, in an accredited external quality assurance (EQA) scheme. EQA samples will be analysed within the routine laboratory workload, by personnel who routinely test patient samples, using the same primary methods as for patient samples.

**Standard 5-6**

Quality metrics

A complete and accurate report containing prescribed quality metrics must be provided at regular intervals to CervicalCheck.

Complete data at least quarterly, within one month of end of period.

**Note:** The quality metrics collected during internal quality control procedures are used for monitoring, assessment, reporting, review and feedback purposes.

The quality metrics required are detailed in the current version of the 'HPV 1 Report'. They include measures, which should be readily available from the laboratories internal quality control processes. Laboratories will have the ability to separate CervicalCheck workload from other workload(s) for statistical and monitoring purposes.

**Quality requirement**

Quality metrics improvement

Laboratories will undertake appropriate and timely measures to address performance issues that impact upon quality metrics and cause values outside of laboratory, national and/or international norms. EQA results will be evaluated on an ongoing basis, with prompt corrective action taken for unacceptable results.
Quality assurance visits
Laboratories will accommodate on-site visits by NCSS-designated personnel for quality monitoring, audit and assurance purposes, providing access to personnel, resources, processes, documentation and results.

5.3 References


8. CervicalCheck Cervical Screening Register (CSR) information system data entry standards demographic details (CS/PUB/REG-2).

9. CervicalCheck Cervical Cytology Form (CS/F/LAB-2).

10. CervicalCheck combined cytology and HPV form (CS/F/LAB-14).


17. CervicalCheck cytology terminology table (CS/PUB/LAB-2).

18. Pathology laboratories HPV testing HPV 1 Report (CS/F/LAB-15).
The National Cancer Screening Service is part of the Health Service Executive. It encompasses BreastCheck – The National Breast Screening Programme and CervicalCheck – The National Cervical Screening Programme, BowelScreen – The National Bowel Screening Programme and Diabetic RetinaScreen – The National Diabetic Retinal Screening Programme.