Quality Assurance and Continuous Quality Improvement in Laboratories which Undertake Cervical Cytology

CYTOTRAIN • LEONARDO •

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PREFACE

One of the key aspect of cervical cancer screening which determines its success or failure is the quality of the cervical smear interpretation. The importance of diagnostic accuracy and reliability can never be overemphasised; the main purpose of quality activities in the cytopathological laboratory should be the maintenance, monitoring and continuous improvement of diagnostic accuracy, i.e; the reduction to a minimum level of the rates of false negative and positive reports.

The present handbook outlines the scope, components and instruments of continuous quality improvement and quality control. In particular it describes in detail Internal Quality Control procedures. It deals also with External Quality Control Schemes, Proficiency and Aptitude testing.

A short outline of accreditation system and quality indicators and standard is also presented.

The included guidelines are intended for personnel involved both in primary screening and in supervision.

They are not to be rigid, but to be seen as indications which may be adopted flexibly according to local decisions.

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1. INTRODUCTION

The Papanicolaou smear test is performed worldwide in order to detect cervical cancer at its earliest stages when treatment is most effective and death can be prevented. Recent epidemiological studies show that regular screening using the Papanicolaou smear test saves many lives. However, to ensure that the test is effective, the cervix must be sampled with care, the smear prepared and processed correctly, analysed and reported by the laboratory with a high degree of accuracy.

This manual is concerned with the issues of diagnostic accuracy and reliability in reporting cervical smears and, as such, is concerned mainly with those aspects of the processing and analysis of cervical smears which are the responsibility of the laboratory. It is intended to minimise the risk of errors of reporting by recommending the quality control measures which should be in place in every laboratory undertaking cervical screening in order to provide a high quality service. It also describes quality standards that must be maintained in order to ensure that the public receive an efficient and effective cervical cancer screening service.

The manual addresses mainly quality issues from the time the cervical smear is received by the laboratory to the time the report is issued. Attention is also given, at the end of the document, to other important aspects of cervical screening such as training requirements, accreditation, certification, management commitment and quality organization.

2. CONTROL, ASSURANCE MANAGEMENT AND CONTINUOUS IMPROVEMENT OF QUALITY

The set of measures designed to ensure the accuracy of interpretation and reporting of cervical smears is termed *Quality Control (QC)*. The quality control measures described in this handbook are widely accepted internationally.

The process of building quality control into a system is termed *Quality Assurance (QA)*. It is intended to build confidence in the product and make it likely that it complies with established standards. In the cytology laboratory quality can be *maintained* by continuous monitoring of laboratory performance and *measured* against a set of agreed quality standards. The standards can be agreed at local, national or international levels: the standards suggested in this manual are intended only as a guide for laboratory managers. They can (and should) be modified according to local laboratory practice.

The most outstanding theoretician of Quality Assurance in the field of health-care is Avedis Donabedian who in 1988 has proposed the partition in three elements of clinical practice - ***Structure, Process and Outcome***. Fig.1 shows how these concepts can be applied to a cytology laboratory.

The term *Quality Assurance* recently has been replaced by the term *Continuous Quality Improvement (CQI)*. It includes traditional *assurance* but has a wider scope. It involves not only taking corrective action, if the laboratory falls below an agreed standard, but also setting new and higher standards, once the original targets have been

Fig. 1 - Structure, process and outcome in the cytopathological lab

STRUCTURE

a. Resources (staff number and qualification, equipment)

b. Organisation (availability of a mission and vision statements, availability of job descriptions, clarity of hierarchical relationships, policies to develop and update procedures and to monitor their implementation)

PROCESS

a. Workload and productivity (e.g. number of slides processed per year by the laboratory and examined per day by individual cytoscreener)

b. Quality of data collection (i.e. reliability, accuracy, completeness of data), of final reporting and recording

c. Implementation of internal and external quality control

OUTCOME

a. Diagnostic accuracy and reliability

b. Timeliness of diagnosis (i.e. time from intake to

achieved, so that the quality of the service can be enhanced even further.

In order to implement a CQI programme a number of elements must be in place (Fig.2).

This document concentrates on the factors which affect the accuracy and reliability of the smear report.

2.1 Sources of error in the cytology laboratory

Errors associated with the cervical screening programme are of two main types: a) those associated with smear taking and preparation b) those associated with microscopic analysis and reporting the smear.

The reporting errors are of two main types: *false negative* reports and *false positive* reports.

False negative reports occur when the cytologist fails to detect cancerous or precancerous cells in the smear.

False positive reports are the results of a misinterpretation of negative smears which are reported as containing abnormal cells.

Both types of error have serious consequences for the woman concerned.

False negative reports are particularly harmful for the patient as they result in a failure to treat the patients disease. The situation may be worsened by the fact that both the clinician and the patient may develop a false sense of security that may delay their concern about the onset of symptoms.

False positive reports cause unnecessary psychological distress and lead to over-treatment. The most important measurements of quality in cytology are **accuracy** and

Fig. 2 - Managerial requisites of a CQI programme

1 **Management commitment**. Without it, quality activities are doomed to remain fragmented and intermittent. Coping with problems only after they have occurred will prevail over prevention and performance improvement.

2 **Delineation of clear responsibility and assignment of adequate resources to quality activities** (time, secretarial and statistical help). It may be advisable to appoint a *quality co-ordinator or facilitator* and a *quality committee* with the participation of all staff categories, under the chairmanship of the laboratory director or his/her closest collaborator.

3 **Training and education** of all staff in basic principles of CQI

4 **A human resource management policy** which includes rewards for the participation in quality activities as well as in professional training.

5 **Periodical review of the quality system**; particular attention should be given to the implementation of corrective measures and the assessment of their effects.

reliability of reporting.

1) ***Accuracy*** can be defined as the level of agreement between the diagnoses offered by the laboratory and the ***Gold Standard***. For cervical cytology, histology is usually accepted as the Gold Standard, but colposcopy or a consensus diagnosis may also be used as Gold Standard. The accuracy of a test is measured by the evaluation of:

- ✔ ***sensitivity*** (ability to identify *true positives*) and
- ✔ ***specificity*** (ability to identify *true negatives*).

Accuracy can also be evaluated by the *positive predictive value* and *negative predictive value*. It can also be expressed as a *false negative* and *false positive rate*. For a precise definition and a numerical example, see appendix 1.

2) ***Reliability*** can be defined as the level of agreement between repeated measurements of the same cytological samples.

Where reliability is concerned, one can distinguish between *intra-observer* variability (the same cytologist can produce different reports for the same cytological sample at different times) and *inter-observer* variability (agreement of different observers reporting on the same samples). For the measurement of reliability (Kappa etc.), see Appendix 2.

In the cytodiagnostic laboratory, diagnoses are the result of evaluation and interpretation and are not expressed in quantitative, but in qualitative or, rarely, semi-quantitative terms. In this respect, cytology is different from other disciplines such as clinical chemistry; however this does not fundamentally alter the nature and objectives of diagnostic accuracy and reliability monitoring.

3. APPLICATION OF QUALITY CONTROL MEASURES IN THE CYTOLOGY LABORATORY

The activities of the cytology laboratory can be broken down into 4 stages as shown in fig.3. They include:

- **Specimen reception**
- **Laboratory processing**
- **Microscope analysis**
- **Reporting**

The Quality Assurance activities described below are intended to minimise the risk of errors at every stage.

3.1 Specimen reception

The laboratory may receive smears from two main sources:

- ✔ from women with symptoms and signs suggestive of cervical cancer, e.g. inter-menstrual or post menstrual bleeding; these smears are usually taken from women attending a gynaecologist or hospital clinic;
- ✔ from apparently healthy women who are having a smear taken as part of a national or regional population screening programme. These smears are usually taken from women attending well women clinics or family planning clinics.

The smears should be delivered to the laboratory by courier or by post in appropriate containers to minimise leakage or breakage. Efforts should be made to ensure that specimens do not get lost or mislaid.

Errors at the point of reception are usually due to mismatching of smears and request forms. To minimise this risk the receptionist /clerk should be trained to carry out the following duties:

a. Match slide with request form.

b. Ensure request form is completed and slide labelled with a permanent marker.
A minimum data set (woman's name, date of birth, address, senders name and address, last menstrual period and the date the smear was taken) should be agreed on with the smear takers. If key information is missing, the receptionist should contact the smear taker to obtain it.

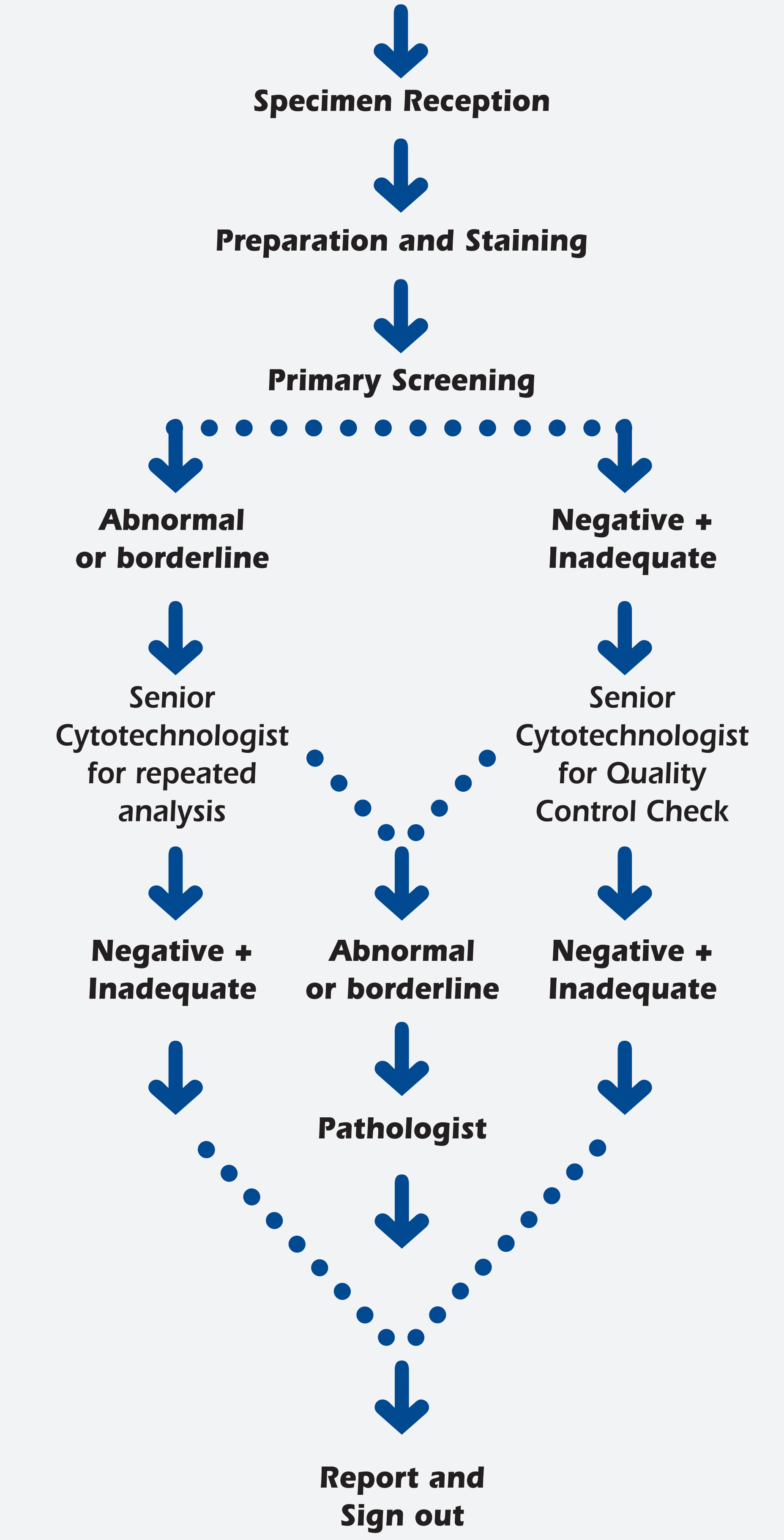
c. Deal with broken or unlabelled smears, following standard operating procedures

d. Enter Personal Identification Data and date of receipt in a computer data base or laboratory register and assign specimen number.

The following QA measures are suggested:

1. Written Standard Operating Procedures (SOPs) in place to ensure receptionist/clerk is

Fig. 3 - **MODEL CERVICAL CYTOLOGY WORKFLOW**



aware of his/her duties

2. Regular rotation of duties so that the clerk or receptionist is not involved in slide/request matching or computer data entry for more than 2 hours at a time.
3. Restriction of computer data entry to 8 data sets / hour.
4. Weekly checks by laboratory manager of accuracy of data entry, e.g. not more than 5 mistakes per 100 entries.
5. The introduction of a bar code system and the standardisation of the cytology request /report form can reduce the risk of error and are strongly recommended.

3.2 Laboratory processing (staining and coverslipping of cervical smears)

It must be stressed that in many cases, false negative reports are issued because of poor quality staining of smear resulting in abnormal cells being missed by the screener. Occasional false negative reports have been issued when abnormal cells lie outside the area of the coverslip.

The following Quality Control and Quality Assurance measures are suggested:

1. Standard operating procedures (SOP) in place to ensure staining protocols are adhered to, equipment is maintained, all reagents (including fixatives) and stains are clearly labelled and stored under appropriate conditions, arrangements are in place for the disposal of reagents and broken slides, regular replacement of stains (e.g. once every two weeks)
2. A daily record is kept of the need for topping up fixatives and stains and the replacement of stains. Stain may need to be replaced more frequently in hot weather or if there is a large throughput of smears.
3. Optimal coverslip size and thickness is agreed (24x50 mm minimum is recommended and coverslip thickness should be no more than 0.17 mm). Plastic film may be used providing it meets the criteria above.
4. Senior laboratory staff undertake daily checks of the quality of staining, i.e. intensity of nuclear staining, contrast between eosinophilic and cyanophilic staining of cytoplasm, definition of nuclear chromatin, quality of dehydration of slide and clarity of mountant.
5. The laboratory complies with health and safety requirements.
6. A random selection of smears should be checked at yearly intervals to determine the extent of fading of the stain and inadequate dehydration. Well-stained slides should maintain their colour intensity for at least three years.
7. Slide files should be checked random at 6 months intervals to ensure that slides can be readily retrieved, if necessary.

3.3 Protocol for microscopic analysis of cervical smears

The *first analysis* or *primary screening* of cervical smears in the light microscope is a demanding and repetitive task requiring intense and prolonged concentration by the cytologist as he / she proceeds to examine and evaluate every cell in

the smear. The task is made more difficult by the fact that the cytologist may be required to detect a relatively low number of abnormal cells, occasionally fewer than 50, scattered among large numbers of normal cells. Since most smears contain between 300,000 and 500,000 normal epithelial cells, the risk of screening error is high.

Traditionally, the initial microscopic analysis of cervical smears (*primary screening*) is undertaken by ***cytotechnologists***. These highly skilled non-medical professional personnel are trained to interpret the smears and prepare a preliminary report. As they may be expected to analyse up to 50 slides a day, habituation and transient loss of concentration can lead to errors of interpretation and failure to recognise abnormal cells.

Usually a more experienced cytologist (a senior cytotechnologist or biologist or cytopathologist acting in a supervisory role) is appointed who is responsible for checking the *smears examined* by the primary screener. However, if cytotechnologists have adequate experience, they may check each other.

This second level of checking is designed to reduce the number of false negative reports which are issued by the laboratory.

A model tiered screening system is shown in fig. 4.

All positive and dubious smears have then to be examined by an authorised person (usually a ***pathologist***) in order to ascertain the diagnosis.

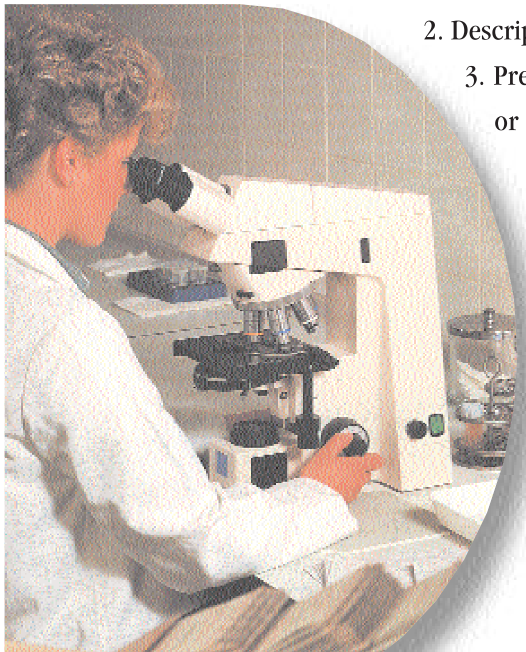
Several methods of quality control have been developed which can be applied on a ***daily and periodical basis (Internal Quality Control)*** and are described in chapters 4 and 5. Each method has its advantages and disadvantages but all may have an important role to play in maintaining laboratory standards.

3.4 Reporting

The report should be prepared with a great deal of care, using a terminology which is clearly understood by the clinician as well as the cytologist. The chosen terminology should also be recognised at national and international level.

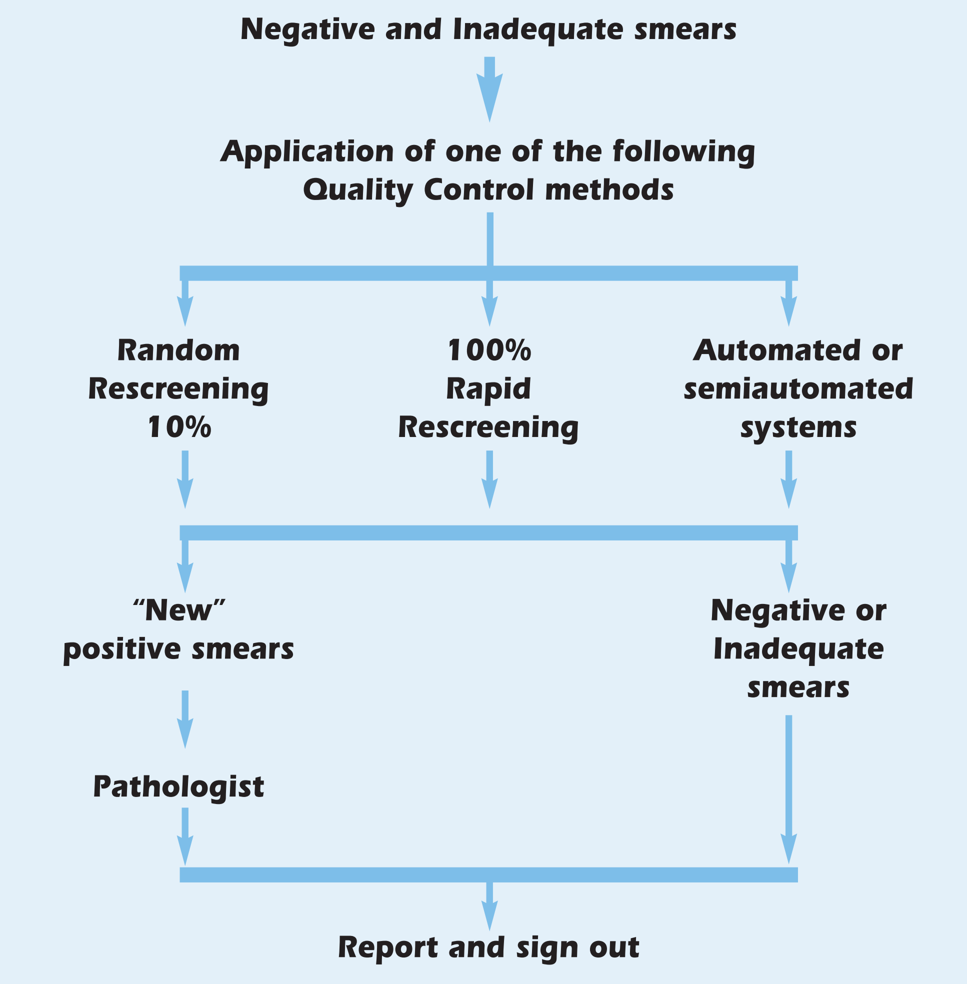
The report should include three parts:

1. Statement of adequacy;
2. Descriptions of cell content;
3. Predicted histological state of the cervix e.g. normal or neoplastic.



A fourth part of the report includes suggestions for management of the patient, but this is optional. The cytologist should take into account all the relevant clinical data concerning the patient before preparing his report.

Fig. 4 - QUALITY CONTROL CHECK OF NEGATIVE AND INADEQUATE SMEARS AFTER PRIMARY SCREENING



4. INTERNAL DAILY QUALITY CONTROL PROCEDURES

4.1 Systematic assessment of smear adequacy

The adequacy of the Pap smear is a crucial point largely affecting the sensitivity of the test.

Well-defined criteria of adequacy should be in place to minimise the variability of evaluation among the screeners. We suggest that laboratory, in accordance with national or international guidelines, should adopt a set of criteria similar to or even stricter that the ones which are laid down in the Bethesda System.

To be considered "***satisfactory for evaluation***" the smear should meet the following criteria:

- appropriate labelling information;
- well-preserved and well-visualised squamous cells should cover more than 10% of the slide surface;
- at least 50% of epithelial cells smeared should be evaluable;

- an adequate transformation zone component: a minimum of 2 clusters of well-preserved endocervical and/or squamous metaplastic cells, each cluster composed of at least 5 appropriate cells (Fig. 5,6);
- clinical information should be available (at least age and last menstrual period).

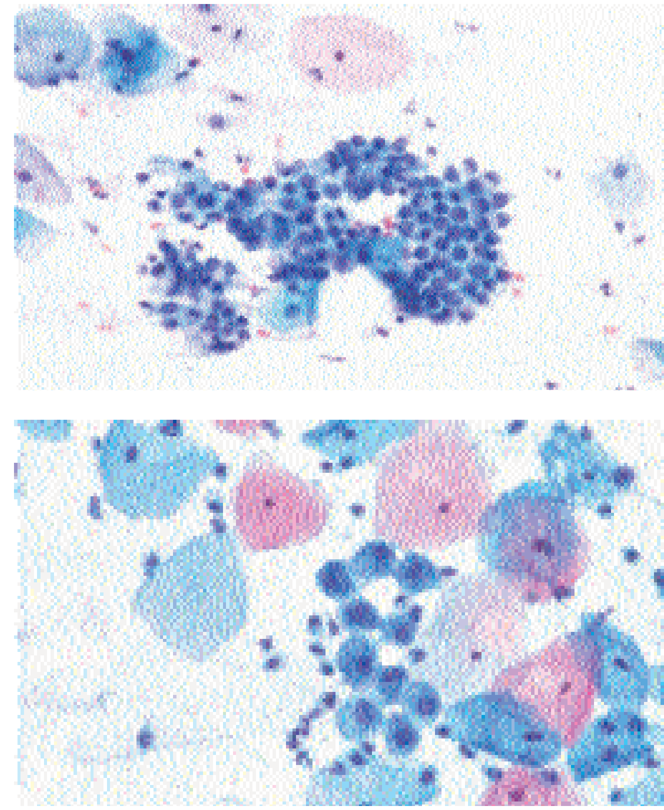


Fig. 5,6 - Two examples of optimal cervical sampling: squamous epithelial cells (superficial and outer intermediate), endocervical and metaplastic cells. 200x

In post-menopausal women with marked atrophic changes and with the squamocolumnar junction moved up, a smear can be considered adequate even if endocervical cells are not recognisable.

A smear should be considered "***unsatisfactory for evaluation" or inadequate*** when it meets the following criteria:

- lack of patient identification
- scant squamous epitelial component: less than 10% of the slide surface
- obscuring blood, inflammation, excess of cytolysis, thick areas, poor fixation, air-drying, contaminant which precludes interpretation of approximately 75% or more of epithelial cells (examples of inadequate smears Figures 7).

A smear containing abnormal cells should never be categorised as inadequate.

The inadequate smear must be repeated.

4.2 Supervisory review of borderline and abnormal smears

All borderline and abnormal smears must be re-examined and reported by a pathologist or an authorised person.

A written Standard Operating Procedure should identify the persons responsible for re-examining and reporting the cases judged borderline or abnormal after the primary screening stage. Traditionally this is the duty of the pathologist but another authorised person, in accordance with national guidelines, will do.

4.3 Supervisory review of all cases with selected clinical characteristics

Smears from patients with a clinical history of abnormal bleeding, e.g. post-coital, inter-menstrual or post menopausal bleeding should be reviewed usually by a senior cytotechnologist as well as those from women with symptoms or signs suggestive of cervical cancer, or who have a past history of pre-invasive or invasive cervical cancer.

4.4 Quality control of negative and inadequate smears

4.4.1 Random rescreening

This method is widely practised in the United States in order to comply with the Clinical Laboratory Improvement Act (CLIA) passed in 1988.

It involves supervisory staff rescreening a random 10% of all smears which have been identified as negative or inadequate by the primary screener. The whole slide should be examined, allowing approximately 6 minutes per smear.

Any abnormality missed by the primary screener should be recorded.

Random rescreening has been severely criticised because it cannot identify all false negatives smears and for statistical reasons it is unlikely to detect substandard performance of the primary screener, in view of the relatively low rate of abnormal smears in a well woman population. Nevertheless, this approach has its advocates, who emphasise that it has the great advantage of increasing awareness of the risk of error in day to day practice.

Krieger, who has extensive experience in this method of quality control and is the director of a large laboratory that processes over a quarter of a million smears annually, claims that random rescreening of 10% of negative smears can be an effective method of improving laboratory performance. He found that the percentage of false negative smears fell from 11% to 5% over 10 years.Krieger argues that, in order to be able to draw statistically valid conclusions, a minimum number of slides needs to be rescreened. This minimum number will depend on the prevalence of abnormality in the rescreened population and the proportion of false negative reports the laboratory is prepared to accept. He has prepared tables which can be used to determine the minimum number needed to make valid observations on laboratory performance.

4.4.2 Rapid review

Rapid Review is a relatively new approach which is widely used in the UK. It involves supervisory staff performing a partial review under a low power microscope objective (x10) of all cervical smears reported as negative or inadequate by the primary screener. The time spent on Rapid Review is estimated at 30-60 seconds per smear. If the supervisor disagrees with the opinion of the primary screener, the smear is subject to a full rescreen.

In theory this approach has several advantages over the Random Rescreening method. It allows a general levelling of reporting standards and the establishment of a *screening profile* for each of the primary screeners. Initial studies suggest that Rapid Review is a better method of quality control than Random Rescreening in terms of quality control, in that Rapid Review identifies more false negative reports than 10% Random Rescreening in the same amount of time. Some studies show that Rapid Review may be able to detect 80% of all abnormal smears (low and high grade abnormalities) missed by the primary screener. However the real value of Rapid Review depends on skill, training and experience of the supervisor. It is recommended that an individual cytotechnologist should not perform Rapid Review on more than 20 smears at a time (30 minutes). The following formula should be used to calculate the sensitivity of primary screening with respect to the final report after rapid review of all negative and inadequate smears:

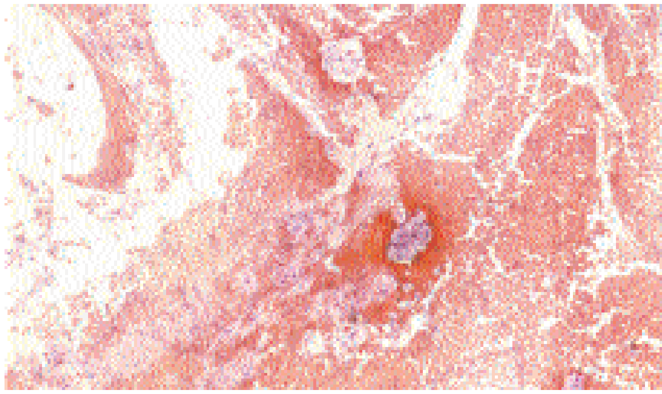


Fig. 7.1 - Excess of obscuring blood. 200x

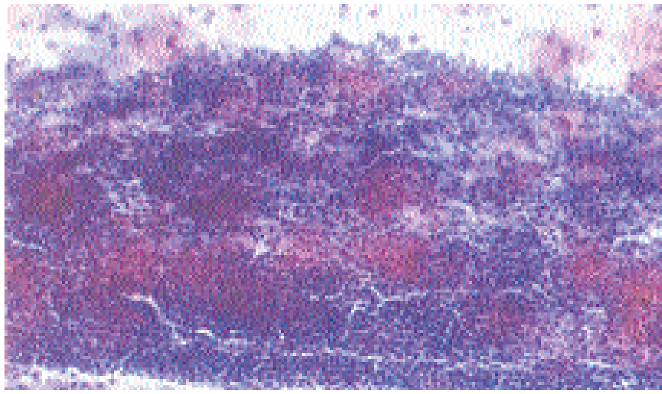


Fig. 7.2 - Excess of inflammation. 200x

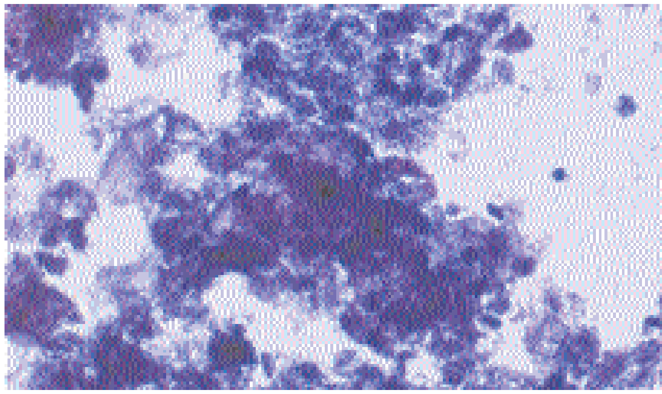


Fig. 7.3 - Excess of cytolysis. 200x

% RELATIVE SENSITIVITY OF PRIMARY SCREENING

$$\frac{\text{Abnormal smears correctly identified by the primary screening}}{\text{Total abnormal smears reported after rapid review}} \times 100$$

A relative sensitivity ≥85% should be aimed if an abnormal smear is defined as suggestive of CIN2 or worse. A lower relative sensitivity is acceptable if the cut-off point for an abnormal smear is borderline or worse.

The precision of the estimate depends on the total number of smears examined by the primary screeners. The calculations may be misleading if they are applied to small numbers.

(To compute confidence interval, the simplest way is to use the programme Epitable of the statistical package EPIINFO, which is available

on the Website: www.cdc.gov).

4.4.3 Automated and semiautomated systems

The American Food and Drug Administration has, to date, approved two automated screening systems for quality control purposes: the PAPNET system (Neuromedical Systems Inc) and the AUTOPAP system (Neopath Inc). Both are used for the rescreening of smears that are reported as negative by the primary screener.

The PAPNET system, that left the market in '99, was composed by two components with separate functions: a scanning function and a review function.

Scanning function: an electronic camera mounted over a microscope which scanned the slide. The camera was programmed to select two sets of 64 (total 128) images (or tiles) in each cervical smear which are then recorded on CD-ROM. A special programme selected the most interesting zones, in theory all those containing abnormal cells.

Review function: the images were displayed on a videoscreen and were inspected and evaluated by the cytologist. The smears were sorted out by the cytotechnologist as "negative" or "review" on the basis of these images. Slides triaged as "negative" were dispatched without further investigation. Slides selected for "review" were examined manually under the microscope and reported according to microscopic findings.

The AUTOPAP 300 (Neopath Inc.) is a non-interactive automatic system that can be used both for the review of negatives and primary screening for Quality Control purpose; it examines conventionally prepared cervical cytologic smears and assigns them an atypia score based on mathematical algorithms. The slides are ranked according to their likelihood of containing abnormal cells. The level at which smears are selected for microscopy examination is determined by the operator. Thus the operator may decide which percentage of slides to analyse.

Tha Autopap system was approved for primary screening by the Federal Drug Agency in the United States in November 1998. It is currently being used in this way in Canada, Japan and United States. When used for primary screening, from 25 to 50% of cervical smears are reported without further microscopic examination.

4.5 Peer review and discussion of abnormal smears

Abnormal smears should be collected on a daily basis and passed around to all the cytologists for their opinion. The smears should be reviewed collectively on a multi-head microscope and the various opinions discussed. It is believed this approach can harmonise smear classification.

4.6 QA procedures at the reporting phase

These procedures should deal with the checking of the matching between the report form and the request form.

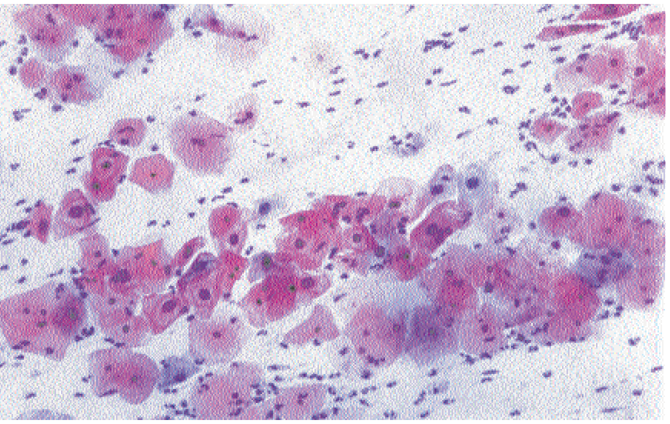


Fig. 10 - LSIL: koilocytes. 200x.

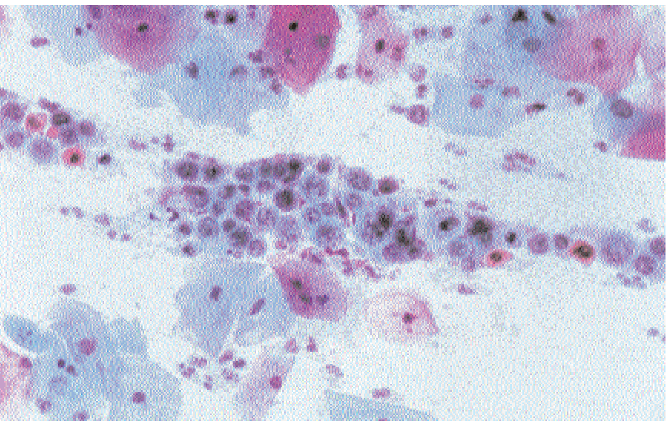


Fig. 11 - HSIL: ca.in situ. 200x

5. INTERNAL PERIODICAL QUALITY CONTROL PROCEDURES NOT APPLIED ON A DAILY BASIS

5.1 Biopsy / cytology comparison

The cytopathologist should review the histology of all cervical biopsies from patients whose cervical smears have been reported by the laboratory.

In cases where there is a major discrepancy between the cytological and histological findings, cases should be discussed with the staff. The number of cases where there is a significant discrepancy should be recorded.

Histological biopsy has long been regarded as the **gold standard** for measuring the accuracy of a cytological diagnosis. The limitations of this method of quality assurance should be born in mind. There are elements of inter-observer and intra- observer variation also in the histological interpretation of cervical biopsies. Besides, results may be influenced by the size of the biopsy, the colposcopist skill and by the type of biopsy. Positive Predictive Values are higher if the histological diagnosis is based on a cone biopsy or a hysterectomy specimen rather than a punch biopsy. It has been suggested that the Positive Predictive Value (*see below and Appendix 1*) of a cytology report of a severe lesion (HSIL) should not be less than 65%.

The positive predictive value of a cytology report of HSIL or worse can be calculated using the following formula:

$$\text{PPV} = \frac{\textbf{Nr of cases of HSILs proved by histology as CIN 2 or worse}}{\textbf{Total number of cases of HSILs or worse}} \times 100$$

5.2 Review of previous smears of women who are found to have an abnormal smears (suggestive of CIN2 or worse) after one or more negative or inadequate smears

It should be a standard laboratory procedure to review previous negative smears from women with an abnormal smear suggestive of CIN2 or worse. False negative smears should be identified and discussed.

5.3 Review of smear history of each woman with diagnosis of invasive carcinoma

The laboratory should identify its *sentinel events*, i.e. those for which an in-depth confidential inquiry is to be undertaken every time they occur, in order to verify what has happened and ascertain whether there have been preventable factors, i.e. possible errors, oversights or delays that may be rendered less probable in the future, thus reducing the risk of such events occurring again. It is not a question of finding the guilty party but, we repeat, one of seeking to render the undesired event less probable in the future.

Cases of invasive carcinoma appearing in women whom were previously tested by the laboratory may be considered sentinel events. The labs, at least those involved in screening programmes, should take steps to obtain the names of women in whom an invasive cancer of the cervix is diagnosed, from histology laboratories and/or the area's tumour registry.

For each case of this type, if the lab has examined one or more smears, all the smears should be re-examined and discussed, similarly to what was stated in section 5.2, but even more in depth, seeking to understand what has happened. An attempt should be made to distinguish the cases that can be attributed to previous diagnostic errors to inadequate sampling to the long time interval between the last Pap test and the diagnosis of invasive carcinoma from the so-called interval cases, i.e. tumours that appeared after an adequate smear dating from no more than 5 years earlier, which had produced an accurate negative report.

5.4 Statistical monitoring of laboratory performance

Statistical monitoring of laboratory diagnoses refers to the evaluation **of the relative distribution of diagnostic categories of the laboratory as a whole and for individual cytotechnologists**.

It involves using a limited number of diagnostic categories (Bethesda or Equivalent Terminology) and analysing the *reporting profile*. Computerised record systems make this form of monitoring much more feasable.

An acceptable profile for a laboratory involved in a screening programme is shown below:

- HSIL (CIN 2 and CIN 3) 1.6% ± 0.4
- LSIL (HPV and CIN 1), ASCUS and AGUS 5.5% ± 1.5
- Inadequate 7.0% ± 2.0

The comparison between cytotechnologists is possible only if slides are given to individual cytotechnologist in a way that avoids selection biases. Given this limitation, if a cytotechnologist shows a consistent excess or deficit of one particular type of reporting category, investigation into the cause is warranted.

When undertaking such an analysis the diagnostic categories most likely to show the greatest variation from the norm are "inadequate" smears and "ASCUS or AGUS".

Laboratory consensus on what constitutes an *inadequate smear* or a *borderline smear* can sometimes resolve these problems (see Glossary).

5.5 Seeding of abnormal smears into the cytology workload

This method aims also at increasing cytoscreener concentration and identifying cytotechnologists with unsatisfactory performance. It involves inserting known positive cases randomly among the routine smears to be screened. Although attractive in principle, it is complicated in practice, and only few laboratories have ever attempted this approach.

The results may vary depending on whether the screeners are aware that this has taken place. Bosch et al. introduced positive smears, previously diagnosed as negative, into the routine workload of 5 screeners, who were unaware of the experiment, and found that the abnormal smears were recognised in only 1 out of 25 cases. When the experiment was repeated with the full awareness of the screeners, all the false negative smears were recognised as positive by three of the screeners, whereas the remaining two continued to make errors.

Hill seeded 240 slides of which 167 abnormal into the laboratory workload over a period of 18 months. A false negative rate of 7.8% was observed for all grades of abnormalities and a false negative rate of a 4.2% for smears with HSIL or worse.

Ronco et al. seeded in the daily work of 5 screeners (and 3 supervisors) a standard set of 28 negative smears and 113 abnormal smear which had been histologically confirmed. Sensitivity of the screening was 88%.

We suggest that this method may be used occasionally, but not systematically, to assess screening quality and to maintain the staff level of concentration.

5.6 Control of workload

Laboratory staffing and workload ratios should be maintained at acceptable levels.

The European Federation of Cytology Societies (EFCS) has suggested that one cytotechnologist may be expected to screen no more than 7,000 smears annually. One full time supervisor is required for every five full time cytotechnologists working in the laboratory.

It has been suggested that in order to maintain their diagnostic skills the minimum annual workload for an individual screener should be 3,000 smears.

5.7 Storage of slides

Standard Operating Procedures (SOPs) must be in place for the filing and storage of smears. Positive smears should be stored for 20 years and negative smears for 10 years.

5.8 Handling of complaints

There should be a procedure that facilitates the forwarding of complaints by the various customers and regulates their handling. Complaints should receive a written response within a short period of time.

It should be pointed out that, according to the total quality, the complaint is a sort of gift that the unsatisfied customer gives the supplier; the truly disappointed customer does not complain, but proceeds to take legal action or limits him-/herself to giving the product bad publicity.

It has also been seen that, if a mechanism facilitating complaints is introduced, at least initially the increase in complaints is associated with an increase in satisfaction.

In other words, contrary to what may be thought, the more unsatisfied customers complain, the more the others are satisfied. Complaints should be classified by type and their long-term trend should be analysed.

5.9 Monitoring of turnaround time

Time of response should be monitored.

No turnaround time (from smear sampling to the report delivery), should exceed 4 weeks and the average turnaround time should be much less.

5.10 Preparation of Annual Report

An annual record of laboratory performance in terms of workload, staffing, distribution of smears in the different reporting categories, biopsy-cytology correlation, accuracy of screening, screening profile and a comparison of these findings and national standards may be useful and should be kept. The information may be compounded in the form of an Annual Report.

Fig. 9 - QUALITY ASSURANCE PROCEDURES

1. INTERNAL QUALITY CONTROL PROCEDURES

On a daily basis

- *Systematic assessment of smear adequacy*
- *Supervisory review of borderline and abnormal smears*
- *Supervisory review of all cases with selected clinical characteristics*
- *Quality control of negative and inadequate smears should be performed by one of the following methods:*
  - *Random rescreening 10%*
  - *Rapid review 100%*
  - *Automated systems 100%*
- *Peer review and discussion of abnormal smears*
- *QA Procedures at the reporting phase*

Periodical (not applied on a daily basis)

- *Biopsy / cytology comparison*
- *Review of previous smears of women who are found to have abnormal smears (suggestive of CIN2 or worse) after one or more negative or inadequate smears*
- *Review of smear history of each woman with diagnosed invasive cervical cancer (sentinel event)*
- *Statistical monitoring of laboratory performance*
- *Seeding of abnormal smears into the cytology workload*
- *Control of workload*
- *Storage of slides*
- *Handling of complaints*
- *Monitoring of turnaround time*
- *Preparation of Annual report*

2. EXTERNAL QUALITY CONTROL PROCEDURES

- *Exchange of slides scheme*
- *Proficiency Testing Schemes*
- *Accreditation and certification*

3. OTHER IMPORTANT MEASURES THAT ASSURE THE QUALITY OF CERVICAL SCREENING

- *Training, certification and continuing professional*

6. EXTERNAL QUALITY CONTROL PROCEDURES

6.1 Exchange of slides scheme

The core of external quality control is the exchange of slides, at regular intervals, between different laboratories. Each laboratory's diagnoses are compared with the diagnoses of the other participating laboratories and with the relevant histological diagnoses. Reproducibility can be evaluated using a *Kappa score* and through other *simple indices of variability* (Appendix 2).

The inter-laboratory slide exchange and comparison is helpful in increasing diagnostic consistency and has also a educative function through the dissemination of information regarding diagnostic approaches and technical and managerial procedures.

In order to be effective, a slide exchange programme in cervical cytology should have the following 10 recommended features:

1. it should be organised on a local or a regional basis, so that the exchange of slides between laboratories is easier and quicker;
2. use of different sets of slides, each with a full range of diagnoses including inadequate and borderline smears, where variability is greatest;
3. selection of slides from authentic patient files with positive diagnoses confirmed by histology;
4. use of a standardised report form;
5. examination of the slides by one or more cytotechnologists and then by a supervisor/pathologist, so that an internal comparison may also take place in each laboratory;
6. fixed response time, e.g. no more than 14 days;
7. diagnoses from the co-ordinating centre should be exchanged by fax (or E-mail), to allow slides with a diagnostic difference to be re-examined before returning them;
8. results and discordant slides should be discussed in periodical local workshops at the microscope with the participation of most staff;
9. statistical analysis both of reliability and accuracy (for slides where a consensus diagnosis has been reached), using also immediately understandable indices (Appendix 2). Accuracy (i.e. sensitivity and specificity, see Appendix 1) should be evaluated only for slides where a consensus diagnosis can be reached, preferably if it coincides with the histological diagnosis;
10. confidentiality of the laboratory results, except when a laboratory consistently performs badly for a number of years.

6.2 Proficiency Testing Schemes

This scheme was introduced in 1968 in the United States and 20 years later in the United Kingdom to monitor the ability of medical and non-medical staff in interpreting cervical smears. The scheme was designed to achieve an unbiased assessment, by an independent external assessor, of the performance of all grades of staff. Papanicolaoustained cervical smears, selected specifically for assessment purpose, are taken by a facilitator to each cytology laboratory participating in the scheme. Each staff member in the laboratory performing cervical screening is given 10 slides and asked to report on them within 2 hours. The facilitator marks the test and informs the participants of the results. Tests are taken twice yearly. The overall laboratory performance in the test is compared with that of other laboratories in the region, usually on an anonymous basis. Experience in the UK has shown that the scheme is useful in detecting unacceptable levels of performance. Personnel falling below acceptable levels are not permitted to screen again until they have attended further training and demonstrated their competence to analyse the smears.

6.3 Accreditation and certification

Accreditation is a process by which a committee of experts, appointed by an independent agency, evaluates and certifies whether an institution, or laboratory, satisfies predetermined requirements (standards), which have been previously agreed by a peer group. By declaring a defined standard of practice and having this independently confirmed, accredited organizations are able to attain a hallmark of performance and offer reassurace to users of their service. Accreditation has to be renewed at fixed periods.

All accreditation programmes require that the laboratories should implement a quality system.

A person responsible for the quality programme within the laboratory must be appointed by the management of the laboratory and report directly to management.

Among the accreditation certification procedures, the most important for laboratories in Europe are the certification ISO 9000 and the Clinical Pathology Accreditation, (UK) Ltd. (CPA).

According to ISO 9000, which is an internationally based certification programme, all the important documentation should be collected in a ***Quality Manual*** that should include:

a. the quality policy;
b. the organisational chart of the laboratory;
c. the job descriptions of all staff;
d. the human resource management policy, including continuous education and the reward system;
e. all written procedures, with special regards to those related to quality control, to the handling of complaints by laboratory users and to equipment maintenance;
f. the organisation and responsibility for quality activities.

The Manual should be constantly updated.

A recent development concerns the preparation of accreditation manuals also for whole screening programmes, not only for individual laboratories.

It is desirable that all EU member countries should activate procedures for accreditation of cytopathological laboratories involved in population screening (see the document: Europe against Cancer).

7. OTHER IMPORTANT MEASURES THAT ASSURE THE QUALITY OF CERVICAL SCREENING

7.1 Training,certification and continuing professional education of cytotechnologists

The skill and experience of the cytotechnologist engaged in cervical screening has an important impact on the quality of the reports issued by the laboratory,

The issue of training has been addressed by the International Academy of Cytology (IAC) and by EFCS and has been discussed in several publications.

It is widely agreed that cytotechnologist training must equip them for the screening of cervical smear, i.e.:

a. the preparation of a descriptive report on all smears that are negative for pre-cancerous changes using a nationally (or internationally) agreed terminology;
b. the identification and reporting of inadequate smears;
c. the identification of suspicious and abnormal smears.

It has been suggested that cytotechnologist should screen a minimum of 5,000 smears under close supervision before being allowed to sign out reports.

In addition, cytotechnologist may be trained in other aspects of cervical cytology such as the reception and recording of patient data and computerised systems. They should be able to carry out general laboratory procedures such as slide staining, mounting, filing, labelling and retrieving slides and patient data.They should adhere to health and safety procedures and participate in quality assurance programmes and continuing professional education. Cytotechnologists should have a regional, national or international certificate indicating completion of training and competence in screening.

The **European Federation of Cytology Societies (EFCS)/Quate Aptitude test for cervical cytology** is an international examination which is designed to provide an objective assessment of a cytotechnologists competence to screen cervical smears. The test, established in 1990 by the European Community Training Project for Cervical Cancer Screening (ECTP/CCS) with funding from Europe Against Cancer, has been carried out in several countries including the United Kingdom, the Netherlands, Germany, Denmark, Italy, Austria, Portugal, Slovenia, Hungary and Norway.

The Aptitude Test for cytotechnologists includes:

1. a *written* test (50 multiple choice questions);
2. a *practical* test:
   - *screening* of 10 smears;
   - a "*spot test*" (20 spot diagnoses of marked cells);
3. an *oral* test, if necessary, for borderline candidates or for candidates eligible for diploma with "distinction" (>90%).

The pass mark is 60/100 in all sections.

Successful candidates receive the certificate of aptitude in gynaecological cytotechnology.

The total number of Aptitude Tests carried out in Europe is until now 486 with a success rate of 78%.

Fig. 12 - QUALITY STANDARDS FOR CERVICAL SCREENING (NHSCSP United Kingdom dat, Ref. 36,1996)

INDICATORS	THRESHOLD
Organization	
Women aged 20-64 screened at least once every 5 (or 3) years (coverage)	>80%
Proportion of women receiving results in 4 weeks from the date of smear taking	>80%
Proportion of women receiving results in 6 weeks	100%
Participation of staff in proficiency testing schemes	100%
Waiting time less than 4 weeks for colposcopy assessment: women with HSIL (CIN 2, CIN 3) or worse	≥90%
Waiting time less than 8 weeks for colposcopy assessment: all referrals	≥90%
Technical process and intermediate outcome	
Presence of cytological evidence of sampling from Transformation Zone (TZ) (metaplastic and/or endocervical cells)	>80% smears
Sensitivity of primary screening with respect to final report after rapid review of all negative and inadequate smears	85-95%
Proportion of slides with lesions of: • HSIL (CIN2 and CIN3)	1.6% ± 0.4
• LSIL (CIN1 and HPV) and ASCUS and AGUS	5.5% ± 1.5
• Inadequate	7.0% ± 2.0
Positive predictive values of cancerous lesions by CIN2 or more severe diagnoses	65-85%
Agreement between cytology and histology	Enquiry in all cases of disagreement leading to different treatment
Workload	
Number of screening programme slides processed / reviewed annually by:	
1. Laboratory	>15,000
2. Individual screeners (incl. checkers)	>3,000 per primary screener (also not fulltime); 7,500 maximum (fulltime)
3. Individual medical staff	>750 cases reported
Number of new cases managed by each colposcopist per year	>100
Final outcome	
Rate of invasive cancer of the cervix	Confidential inquiry in 100% of cases *Ideally one should distinguish at least between interval cases (i.e. in women who have had "true" negative smear in the previous 3 years) and other cases*
Proportion of women with unknown outcome within 12 months	<5%
Proportion of women treated at the first visit who have evidence of CIN on histology	≥90%

*Fig. 12 - In order to monitoring the process and the outcome of quality programmes, each laboratory should develop a set of **indicators** to be collected sistematically and analised periodically. An indicator which is accompanied by a **threshold** (acceptable or aimed at value) may be called **standard**. We report here a suggested set of standards.*

7.2 Training and experience of the pathologist

Since pathologists are responsible for overall supervision of the cytology service and are required to report all suspicious and abnormal smears, it is important that they receive adequate training in this field. The training of cytopathologists varies from country to country: the ECTP/CCS has recommended that pathologists should have 6 months training in cytology during which time they should attend lecture, screen and report at least 1,500 selected slides (of which many positive and/or controversial) under supervision, have access to a teaching set and slide libraries and correlate all cervical biopsies with the corresponding cervical smear.

Sensitivity	$\frac{a}{a+c}$	= **True positive / (True positive+False negative)**
Specificity	$\frac{d}{d+b}$	= **True negative / (True negative+False positive)**
Positive predictive value* (PPV)	$\frac{a}{a+b}$	= **True positive / (True positive+False positive)**
Negative predictive value* (NPV)	$\frac{d}{d+c}$	= **True negative / (True negative+False negative)**
Rate of proportion of false negative	$\frac{c}{a+c}$	= **= 1-sensitivity**
Rate of proportion of false positive	$\frac{b}{b+d}$	= **= 1-specificity**

**** The predictive values depend on the prevalence i.e. on the number of cases with cervical abnormalities in the relevant population; PPV and NPV can be calculated directly from a table like the one above only when the subjects are a representative sample of the relevant population.***

7.3 Management commitment and quality organisation

As already said, quality activities cannot be implemented systematically without a strong commitment by the top management. The commitment is shown by:

a. a sense of leadership, i.e. the capability to promote a shared effort towards improvement and innovation;

b. the delegation of the daily co-ordination of quality activities to the most reliable and prestigious staff;

c. the linkage between the participation to quality activities and financial and moral rewards;

d. the interest in auditing and improving the quality system

The main features of the quality system may include:

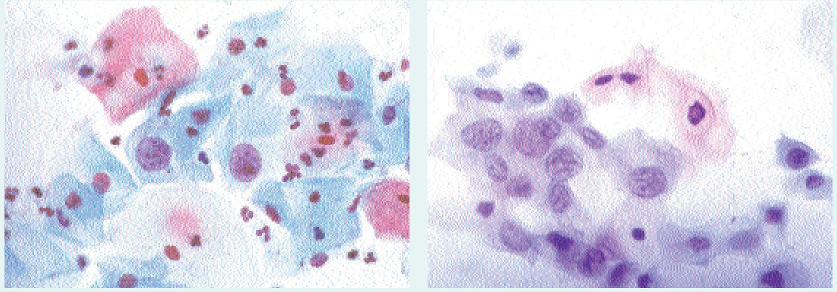
1. availability of a written policy, endorsed by the top management
2. appointment of a quality co-ordinator;
3. implementation of an improvement working group, that is chaired by the quality co-ordinator and includes representatives of all staff categories;
4. development of a set of basic indicators and standards (i.e. indicators plus thresholds) to monitor fundamental features of the lab processes and results (see for instance fig. 12);
5. carrying out of quality evaluation and improvement projects, according to the PDCA phases (Planning, Do, Check, Action) of the so called Deming's wheel of total quality. This includes problem identification, definition of criteria and desirable standards, present situation assessment, pilot corrective action, results assessment, pilot action generalisation (if results were good) and dissemination of the experience;
6. continuous monitoring of the implementation of the selected quality control activities (see before) and of the level of attainment of the defined standards;
7. periodic audit of the quality system.

8. APPENDIX 1
Calculation of sensitivity, specificity, Predictive value and accuracy

TEST	OUTCOME	
	Positive	Negative
Positive	a (True Positive)	b (False Positive)
Negative	c (False Negative)	d (True Negative)

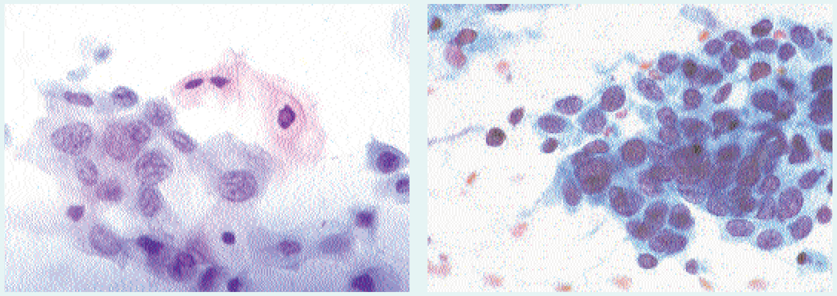
Index A: Diagnostic reliability between CIN 1 + HPV versus CIN 2

$$A = \frac{\text{The greater number between the number of (CIN 1 + HPV) versus the number of CIN 2}}{\text{Total (CIN 1 + HPV) + CIN 2}}$$



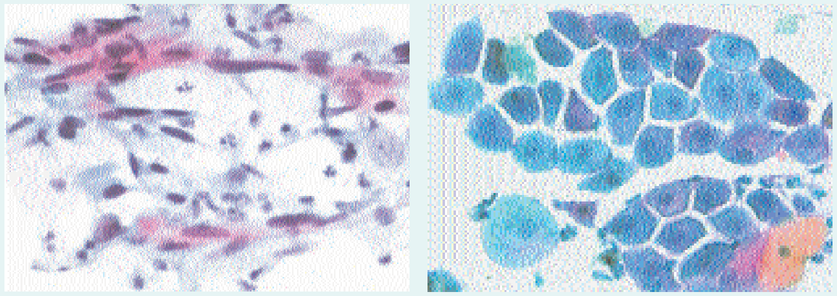
Index B: Diagnostic reliability between CIN 2 versus CIN 3

$$B = \frac{\text{The greater number between the number of CIN 2 versus the number of CIN 3}}{\text{Total (CIN 2 + CIN 3)}}$$



Index C: Diagnostic reliability between CIN 2 + CIN 3 + invasive carcinoma versus CIN 1 + all other diagnoses

$$C = \frac{\text{The greater number between the number of CIN 2 + CIN 3 + invasive carcinoma versus CIN 1 + all other diagnoses}}{\text{Total diagnoses}}$$



NUMERICAL EXAMPLE ON THE SLIDE N. 196 OF THE PAPER

The diagnoses of 14 laboratories are reported

Diagnoses by laboratories		Indices
Negative and other diagnosis	0	
HPV, CIN 1	4	*Index A = 4/(4+3) = 0.57*
CIN2	3	*Index B = 6/(6+3) = 0.66*
CIN 3	6	*Index C = 10/(10+4+0) = 0.71*
Invasive carcinoma	1	
Total	14	

** Branca M. Morosini P.L. , Duca P.G., Verderio P., Giovagnoli M.R., Riti M.G., Leoncini L. et alii. Reliability and accuracy in reporting CIN in 14 laboratories. Developing new indices of diagnostic variability in an interlaboratory study. Acta Cytol. 42:1370-1376, 1998.*

10. GLOSSARY OF TERMS AND ABBREVIATIONS

Accreditation

The mechanism by which an agency or an organisation evaluates and verifies that an organization, service, or a programme of study meet specific predetermined standards

Accuracy

The level of agreement between the diagnoses offered by the laboratory and the Gold Standard. For cervical cytology, histology is usually accepted as the Gold Standard but for consensus among experts may also be used as a Gold Standard. The accuracy of a test is measured as sensitivity (ability to identify true positives) and as specificity (ability to identify true negatives).

Accuracy can also be measured as the predictive value of a test and can also be expressed as the false positive or false negative rate (see appendix 1).

Adequate smear

In cervical cytology, adequacy is the set of criteria which the smear must meet to be considered suitable for diagnosis.

Many factors can make a smear difficult to analyse:

- air-drying and poor fixation
- extensive cytolysis
- large number of leukocytes, red blood cells or other contaminants

The assessment of adequacy is a subjective exercise but the following criteria are widely used:

- well-preserved and well-visualised squamous cells should cover more than 10% of the slide surface
- at least 50% of epithelial cells smeared should be evaluable
- transformation zone component: minimum 2 clusters of well-preserved endocervical and/or squamous metaplastic cells, each cluster composed of a minimum of at least 5 cells.

A smear containing abnormal cells should never be categorised as inadequate (the Bethesda System 1991).

It may be emphasized also that all slides should have appropriate labelling and identifying information and be accompanied by relevant clinical information (at least age and last menstrual period).

Aptitude test

An Aptitude Test for cervical cytopathology is an examination which is intended to test in an objective and standardised way the competence of a cytologist to perform the task of cervical screening

Biopsy

A sample of tissue cut from a living body.

In cervical cancer, a screening biopsy of the cervix can be performed under colposcopic control. The biopsy is processed for histological examination

Borderline

This is a term used to describe a smear which is adequate for reporting but which contains epithelial cells which cannot be readily classified as normal or neoplastic. Women with borderline smears are usually kept under observation. The equivalent terminology for borderline smears is ASCUS/AGUS in the Bethesda System.

Certification

The process by which a non-governmental agency or organisation conveys recognition that an individual has demonstrated competence in certain tasks and has met certain predetermined standards specified by that body.

In cytotechnology, those requirements or standards are:

1. Graduation from an accredited or approved school of cytotechnology
2. Completion of a given amount of work experience
3. Acceptable performance on a qualifying examination or in a battery of related examination.

Cervical sampling

Cervical sampling is the procedure by which a representative cellular sample from the ectocervix, transformation zone and endocervix is obtained for microscopic examination.

Errors of sampling affect the sensitivity of cervical screening and can result in a high rate of false negative tests.

The adequacy of smears should be constantly monitored and a system of feedback to the smear taker should be implemented by the cytopathology laboratory.

Colposcopy

Colposcopy is a non-invasive diagnostic procedure performed with an instrument that magnifies the uterine cervix (from 10x to 40x).

It permits the colposcopist to evaluate the transformation zone and also permits:

- evaluation of blood microvessels
- evaluation of suspect Schiller's iodine-negative areas
- assessing the extension and upper limit of the lesion
- performing punch biopsies of abnormal epithelium

Colposcopy is the principle second level examination in a cervical screening programme and it is applied on women with a positive smear.

Confidence interval

It is the interval which contains the population or true value with a certain probability, usually 95% (95% confidence interval). In Appendix 2 confidence limit for proportion calculated on small samples are given. E.g. if in a sample of 10, 2 failures out of 10 tests, were observed, the proportion is 0.2 equal to 20% and the 95% confidence interval ranges from 2.5% to 55.6%. This means in practical terms that the "true" proportion of failures could be as low as 2.5% as high as 55.6%.

Continuous Quality Improvement

Continuous quality improvement (CQI) has now replaced the term quality assurance. It includes traditional quality control in the laboratory but has a wider scope. The aim of CQI is not only the identification and recognition of laboratory errors but also the continuous improvement of the quality of diagnostic services based on monitoring of relevant indicators.

Errors of sampling

See **Cervical sampling**.

Errors of smear preparation

Errors of smear preparation can occur if the correct procedure is not followed by the smear taker.

This type of error can occur either when all the material present on the sampling devices is not entirely and correctly transferred on the smear or when there is delay in smear fixation. Errors of smear preparation affect the sensitivity of cervical screening and can result in a high rate of false negatives and/or inadequate test

External Audit
This usually refers to an independent assessment of the performance of the laboratory, against agreed national or regional standards.

External Quality Control
The core of external quality control is the participation in a slide exchange programme among different laboratories and comparison of diagnosis.

False negative reports
False negative reports are issued when the cytologist fails to detect cancerous or pre-cancerous cells which are present in the smear

False positive reports
False positive reports are issued when the cytologist misinterpret normal epithelial cells as abnormal epithelial cells in the smear

Gold Standard
Reference against which activities or results are measured

Guidelines
Systematic recommendations designed to help operators to choose the best procedure in an expected situation

High Grade Squamous Intraepithelial Lesion (HSIL)
Is a cytological diagnosis introduced by the Bethesda System (1989) to describe abnormal cellular changes in smears which are suggestive of the presence of moderate, severe dysplasia, CIN 2, CIN 3 and carcinoma in situ in the cervix.

Inadequate smear
An inadequate smear is unsuitable for diagnosis.
This type of specimen should be repeated.
A smear should be considered inadequate when it meets the following criteria:

- lack of patient identification
- scant squamous epitelial component: less than 10% of the slide surface
- obscuring blood, inflammation, excess of cytolisis, thick areas, poor fixation, air-drying, contaminant which precludes interpretation of approximately 75% or more of epithelial cells

If abnormal cells are detected, the specimen should never be categorised as unsatisfactory.
(The Bethesda System 1991) (see also Adequate smear)

Internal Quality Control
Internal Quality Control measures are the procedures introduced in the laboratory by the staff designed to ensure accurate results of screening.

Kappa value
A statistical measurement of reliability that takes into account the agreement due to chance. A kappa value of 0 means that all agreement is due to chance.
A kappa value of 0.60 or more is considerate adequate.

Low Grade Squamous Intraepithelial Lesion (LSIL)
Is a cytological diagnosis introduced by the Bethesda System (1989) to describe abnormal cellular changes in smears which are suggestive of mild dysplasia, HPV changes and CIN 1.

Negative Predictive Value
The Negative Predictive Value is the proportion of all individuals tested who are really without disease in relation to all individuals with negative findings or results.

Negative smear
A negative smear is an adequate smear reported as containing only morphologically normal cells. It contains no cells showing pre-malignant or malignant changes.

Papanicolaou test (or PAP test)
The test for the screening of cervical cancer described in this document.
The test was developed by G. Papanicolaou in 1943.

Population screening
See **target population**

Positive Predictive Value
The Positive Predictive Value is the proportion of positive subjects (with a result that suggests the presence of disease) out of all subjects with positive results (i.e. the sum of true positive and false positive).

Positive smear (or slide)
A "positive" smear is a smear containing morphologically abnormal cells (diagnostic for borderline, pre-cancerous or cancerous lesions)
When calculating the accuracy of screening it is important to be clear about the cut off point at which the smear is classified as positive.

Proficiency testing
Scheme to monitor the skill of medical and non-medical personnel in interpreting cervical smears. See paragraph 6.2. According to ISO 43 norm, this term is now being used also to indicate an external Quality Control Programme.

Quality
The characteristics of an entity that bear upon its ability to satisfy stated or implied needs.

Quality Assurance
All the planned and systematic activities implemented, to provide adequate confidence that an entity will fulfil requirements for quality.

Quality Control
See in this document chapters 4,5,6.

Reliability
Level of agreement between repeated measurements of the same object.
In the cytopathology laboratory, reliability can be defined as the level of agreement between repeated measurement of the same cytological sample either by the same observer or different observers.

Reproducibility
See **Reliability.**

Sensitivity
The sensitivity of the test is defined as the proportion of subjects with the disease correctly identified as positive out of all persons with disease: true positives/ (true positives + false negatives).

Sentinel event

Rare severe event that could be caused by remediable factors and prods a confidential inquiry every time it occurs.

Specificity

The specificity of a test is defined as the rate of correctly identified persons without disease in relation to all persons without disease: true negatives/ (true negatives + false positives).

Standard

A required level of quality or proficiency. Also an indicator accompanied by a reference value or threshold.

Standard Operating Procedures

Written descriptions of how a routine operations or activities should be carried, by whom, where and when.

Target population

A group of persons sharing pre-defined characteristics eligible for a particular test or investigation or the object of a particular study.

Transformation Zone (TZ)

Is the name given to area of columnar epithelium which undergoes metaplastic changes to a squamous epithelium.

11. SUGGESTED READINGS

1. O.A.N. Husain, E.B. Butler, D.M.D. Evans, J.E. McGregor, R. Yule: Quality control in cervical cytology. J. Clin. Pathol. 27: 935-944; 1974.
2. Husain O.A.N., Blanche Butler E., Woodford F.P. Combined external quality assessment of cytology and histology opinions: a pilot scheme for a cluster of five laboratories. J. Clin. Pathol. 37:993-1001, 1984.
3. Attwood M.E., Woodman C.B.J., Luesley D., Jordan J.A. Previous Cytology in patients with invasive carcinoma of the cervix. Acta Cytol. 29:108-110, 1985.
4. Roberts A.D., Denholm R.B., Cardiner J.W. Cervical intraepithelial neoplasia in postmenopausal women with negative cervical cytology. Br. Med. J. 290-291, 1985.
5. Gay J.D., Donaldson L.D., Goellner J.R. False negative results in cervical cytology studies. Acta Cytol. 29:1043-1046, 1985.
6. Deming W.E. Out of the crisis, Cambridge . 1986
7. Van der Graaf Y., Voijs G.P. False negative in cervical cytology. J.Clin. Pathol. 40: 438-442, 1987.
8. Romback J.J., Cranendenok R. Velthuis F.J.J. Monitoring laboratory performance by statistical analysis of rescreening cervical smears. Acta Cytol. 31:887-894, 1987.
9. Klinkhamer P.J.J.M., Voijs G.P., Haan A.F.J. Intra-observer and inter-observer variability in the diagnosis of epithelial abnormalities in cervical smears. Acta Cytol 32:794-800; 1988
10. Donabedian A.: The quality of care: how can it be assessed. JAMA 260, 1743-1748. 1988.
11. United States Department of Health and Human Services: Clinical laboratory improvement amendment, 1988.
12. Koss LG: The Papanicolaou test for cervical cancer detection: A triumph and a tragedy. JAMA1989; 261:737-743.
13. Robertson A.J., Anderson J.M., Swanson-Beck J. et al, Observer variability in histopathological reporting of cervical biopsy specimens. J. Clin. Pathol. 42, 231-238, 1989.
14. Robertson AJ et al Observer variability in histopathological reporting of cervical biopsy specimens J Cin Pathol, 42, 231-238, 1989.
15. Quality assurance in cervical cytology. The Papanicolaou smear. Council on Scientific Affairs. Lundberg G.D. Ed. JAMA 262:1672-1679, 1989.
16. Ismail S.M., Colclough A.B., Dinner J.S., Eakins D., et al. Reporting cervical intraepithelial neoplasia (CIN): intra and interpathologist variation and factors associated with disagreement. Histopathology: 16, 371-376, 1990.
17. Branca M., Morosini P.L.: Guidelines for Quality Assurance in Gynaecological Cytohistopathology: the recent advances in Cervical Pathology and Colposcopy. CQ Proceedings of the 7th World Congress of Cervical Pathology and Colposcopy. Rome, May 3, 1990.
18. Soost H.J., Lange H.J., Lehmacher W., Ruffing-Kullmann B. The validation of cervical cytology: sensitivity, specificity and predictive values. Acta Cytol. 35: 8-14, 1991.
19. Jordan S.W. Great expectation: cytology provision of CLIA-88 and the role of professional societies. Cytopathology Annual 235-247, 1992
20. Melamed M.R., Flehinger B.J.: Editorial: re-evaluation of quality assurance in the cytology laboratory. Acta Cytol. 36:461-465, 1992
21. Bosch M.M.C., Rietveld Scheffers P.E.M., Boon M.E. Characteristics of false negative smears. Acta Cytol. 36: 711-716, 1992.
22. O'Leary D.S., O'Leary M.R. From quality assurance to quality improvement. Emerg. Med. Clin. North America. 10:477-92, 1992.
23. Robertson J.B., Woodland B. Negative Cytology preceding cervical cancer: causes and prevention. J. Clin. Pathol. 1993, 46: 700-702.
24. Faraker C.A.: Partial re-screening of all negative smears: an improved method of quality assurance in laboratories undertaking cervical cytology. Cytopathology, 4:47-50, 1993
25. Coleman D.V., Day N., Douglas G., Farney E., Lynge E., Philip J., Segnan N.: European Guidelines for Quality assurance in cervical cancer screening. Europ. J. Cancer 29/A, Suppl.4, S1-30, 1993.
26. The Bethesda System for reporting cervical-vaginal cytologic diagnoses: revised after the second National Cancer Institute Workshop, April 29-30 1991. Acta Cytol. 37: 115-24; 1993.
27. Marsan C., Cochand-Priollet B. L'évaluation de la qualité en cytologie cervico-vaginale. Arch. Anat. Cytol. Path. 3-4:185-186, 1993.
28. Palli, M. Confortini, A. Biggeri, A. Russo, P. Cariaggi, et al.: A quality control system involving peer review of abnormal cervical smears. Cytopathology 4: 17-25; 1993.
29. ISO 8402: 1994 Quality management and Quality Assurance Vocaboulary.
30. ISO 9000-1: Quality management and quality assurance standard. Part 1: Guidelines for selection and use 1994.
31. Ovretveit J.: Health service quality. An introduction to quality methods for Health Services. Blackwell Scientific Pubblications - Oxford. 1994.
32. O'Sullivan, Ismail L.S.M., Barnes W.S.F. et al. Interobserver variation in the diagnosis and grading of dyskaryosis in carvical smears: Specialist Cytopathologist compared with non specialists. J.Clin Path 47, 515-518, 1994.
33. Gifford C., Coleman D.V. Quality Assurance in cervical cancer screening: results of a proficiency testing scheme for cytology laboratories in the North West Thames region. Cytopathology 5, 197-206, 1994.
34. Krieger P and Naryshkin S Random rescreening of cytologic smears: a practical and effective component of quality assurance programs in both large and small cytology laboratories Acta Cytol, 38, 291-298, 1994.
35. O'Sullivan JP et al. Interobserver variation in the diagnosis and grading of dyskaryosis in cervical smears: specialists compared with non specialists. J Clin Pathol, 47, 515-518, 1994.
36. Kaminski F.C., Burke R.J., Haberle K.R., Mullins M.S.: Re-screening policies in cervical cytology and their effects on detecting the truly positive patient. Acta Cytol. 39: 239-245, 1995
37. Dudding N. Rapid re-screening smears: an improved method of quality control. Cytopathology, 6:95-99, 1995
38. Wolfendale M. Internal quality control with reference to rapid re-screening. Cytopathology., 6, 375-367; 1995

39. Syrjanen K.J. Quality Assurance in the Cytopathology laboratories of the Finnish Cancer Society. Compendium of Quality Assurance. 134-141 (1995).
40. Mitchell H., Medley G. Differences between Papanicolaou smears with correct and incorrect diagnoses. Cytopathology 6, 368-375, 1995.
41. Vooijs G.P., A.J.M. van Aspert van Erp, B.E. van't Hof Grootenboer, A.G.J.M. Hanselaar. Parameters of quality control in cervical cytodiagnosis. In: Compendium on Quality Assurance, Proficiency Testing and Workload Limitations in Clinical Cytology. (eds.) G.L. Wied, C.M. Keebler, D.L. Rosenthal, U. Schenck, T.M. Somrak, G.P. Vooijs. Tutorials of Cytology, Chicago, Illinois, USA, pp. 95-107, 1995.
42. McGoogan E. Quality assurance in cervical screening in the United Kingdom: Ensuring that quality continues to improve. In: Compendium on Quality Assurance, Proficiency Testing and Workload Limitations in Clinical Cytology (eds.) Wied G.L., Keebler C.M., Rosenthal D.L., Schenck U., Somrak T.M., Vooijs G.P., Tutorials of Cytology, Chicago, Illinois, USA, 125-133, 1995.
43. The Scottish Office. Report of a working party on internal quality control for cervical cytopathology laboratories. September 1995.
44. Wied GL., Keebler CM., Rosenthal DL., Schenck U., Somrak TM., Vooijs GP. (Edit): Compendium on Quality Assurance, Proficiency Testing and Workload Limitations in Clinical Cytology, Tutorials of Cytology, Chicago, 1995.
45. Coleman D.V. Internal quality control for cervical cytopathology laboratories. Cytopathology. 7, 1-3, 1996
46. Baker A., Metcher D.M.: Rapid cervical cytology screening. Cytopathology 2:299-301, 1996
47. Cocchi V., Sintoni C., Carretti D., Sada D. et al: External quality assurance in cervical vaginal cytology. International agreement in the Emilia Romagna region of Italy. Acta Cytol. 40:480-488, 1996
48. Ciatto S., Cariaggi M.P., Minuti M. et al. Interlaboratory reproducibility in reporting inadequate cervical-smears - a multicentric multinational study. Cytopathology 7: 386-390, 1996
49. Ronco G., Montanari G., Aimone V., Parisio F. Estimating the sensitive of cervical cytology: errors of interpretation and test limitation. Cytopathology, 7: 151-158, 1996.
50. Hill R.M., Dunn P.J.: On the "irreducible false negative rate" in cervical cytology. Diagn. Cytopathol. 15:184, 1996.
51. Marsan C. Frottis cervico-vaginaux et evaluation de qualité. Ann. Pathol. 16, n.5, pp. 344-349, 1996.
52. Pritchard J. et al. Quality Assurance Guidelines for the cervical screening programme. Report of a Working Party, National Health Service Cervical Screening Programme. Publication n. 3, Shieffield 1996.
53. Vooijs G.P. Opinion pool on quality assurance and quality control. Acta Cytol. 40:14-24, 1996.
54. M. Branca M. Duca P.G. Riti M.G., Rossi E. et al: Reliability and accuracy of reporting cervical intraepithelial neoplasia (CIN) in 15 laboratories throughout Italy: phase one of a national programme of external quality control in cervical screening. Cytopathology, 7, 159-172, 1996.
55. Di Bonito L., Falconieri G., Tomasic G., Colautti I., Bonifacio D., Daudine S. Cervical cytopathology: an evaluation of its accuracy based on cytohistologic comparison. Cancer, 72:3002-3006, 1997.
56. Association Francaise d'assurance de qualité en Anatomie et Cytologie Pathologiques (A. F. A. Q. A. P.). Cochand - Priollet B. et al. Recomandation pour l'evalutation de qualité intene des frottis de dépistage du cancer du coll utérine en France dans les structures d'Anatomie et Cytologie Patologique. Arch. Anat. Cytol. Pat. 45, 6: 345-351; 1997.
57. Cenci M. Nagar, Giovagnoli M.R., Vecchione A. "The Papnet System for Quality Control of Cervical Smears: Validation and Limits" Anticancer res. 4731-4734,17, 1997.
58. Gifford C., Green J., Coleman D.V. Evaluation of proficiency testing as a method of assessing competence to screen cervical smears. Cytopathology, 8, 1997.
59. Krieger PA, Cohen T, Naryshkin S A practical guide to Papanicolaou smear rescreens. How many slides must be reevaluated to make a statistically valid assessment of screening performance? Cancer Cytopath 84, 130-136, 1998
60. Branca M. Morosini P.L., Duca P.G., Verderio P., Giovagnoli M.R., Riti M.G., Leoncini L. et al. Reliability and accuracy in reporting CIN in 14 laboratories. Developing new indices of diagnostic variability in an interlaboratory study. Acta Cytol. 42, 1370-1376, 1998.
61. Krieger P.A., McGoogan E., Voijs G.P. et al.: Quality Assurance / control issues International Academy of Cytology Task Force Summary Diagnostic Cytology towards the 21st Century: an International expert Conference and Tutorial. Acta Cytologica 42: 133-140, 1998.
62. Clinical Pathology Accreditation (UK) Ltd. Annual Directory 1999 - Shieffield U.K. 1999.
63. Coleman DV and Evans DMD Quality Assurance in the cytology laboratory In: Biopsy Pathology and Cytology of the Cervix Arnold Publ. 423-426. 1999.
64. Marucci G., Collina G., Damiani S., Dina R., Foschini M.P., Losi L., Roncaroli F., Eusebi V. Controllo di Qualità della Sezione di Anatomia, Istologia e Citologia Patologica "M. Malpighi", Dipartimento di Oncologia, Università di Bologna, Ospedale Bellaria. Pathologica, 91: 268-275; 1999.
65. PRISMATIC Project Management Team. Report on PRISMATIC Trial: A study undertaken to evaluate an interactive automated screening system (PAPNET) for primary screening of cervical smears. Lancet; 353: 1381-85; 1999.
66. Branca M. Coleman D. Marsan C. Pap Test Procedure Leonardo da Vinci - Cytotrain Project 1996-2000, pp 3-20. Contract N.: UK/96/1/40078/P1 IDX N.: 4643.
67. Mody D.R., Davey D.D., Branca M. et al. IAC Task Force No. 14: Quality Assurance and Risk Reduction Guidelines. International Consensus Conference on the Fight Against Cervical Cancer, Chicago March 2000, Acta Cytol. 44:496-507, 2000.
68. Branca M. Test europeo di competenza in citopatologia cervico-vaginale. Pathologica 2001; 93:28-33.
69. Morosini P.L., Perraro F. Enciclopedia della Gestione di Qualità in Sanità, Centro Scientifico Editore, 2001.
70. CPA Website: www.cpa-uk.co.uk.