

Current Research & Reviews on Cervical Cancer

Chapter 2

Quality assurance in reporting Cervical Cytology

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Abbreviations

R-10%: 10% Random Re-Screening; RPS: Rapid Pre-Screening; RR: Rapid Rescreening; 100% RR: 100% Rapid Rescreening; RCRC: Rescreening with Clinical Risk Criteria

1. Introduction

Pathologists play a central role in delivering healthcare which includes cancer screening programmes as Pap test in cervical cytology. Quality is the integral part of any laboratory report. Quality is characteristic of entities that bear upon its ability to satisfy stated or implied needs. Quality control (QC) is the operational techniques and activities that fulfill and verify requirement of quality in an individual test or a process. Technical quality ensures that the products falls within pre-established tolerance limits. QC measures output. QC and organizational structure are complement to each other. It originated in industry as industrial QC which later extended to health care. Initially the QC in medical laboratories started with clinical biochemistry, later it was implemented to other labs and also clinical world [1,2,3]. In cervical cytology quality control is the design which ensures accuracy of interpretation and reporting of cervical smear [4].

The process of building quality control into a system is quality assurance (QA) where the quality is maintained and measured against a set of quality standards [4]. Continuous QC lead to continuous quality improvement (CQI) with respect to time, performance and achievement of a uniform quality. CQI is a continuous process unlike QA which is periodical assessment and focuses on accreditation. CQI is slowly replacing QA. QA includes traditional QC

measures, formation of well coordinated multi-disciplinary professional team, implementation of planned & systematic activities, provide adequate confidence that the entity fulfills requirement for quality, corrective actions for non-conformities from that level, continuous improvement in the quality of diagnostic services, setting of new & higher standards once original targets have been reached giving rise to further enhancement of the quality of the service and high quality. In other words, QA is systematic evaluation of quality control results and quality practice parameters to assure that all systems are working in a manner appropriate to the excellence in health care delivery. QA is a coordinated system to detect, control and prevent the occurrence of errors and finally further the clinician's ability to for quality care of the patients. All the quality assurance processes are to be described and documented in the QA programme manual of the laboratory [1,3].

The QA procedures guarantee that the procedure protocols will be effectively implemented. However QA cannot always guarantee as errors are unavoidable. QA programmes are recognized by accreditation systems which evaluates adequacy of resources, organization of health care institutions and ensure compliance with requirements concerning resources, staff qualification, administrative management and availability of equipment. QA involves global assessment of the process and focuses on the outcome. Outcome in cytology is patient care. QA process includes intradepartmental consultation, diagnostic seminars, microscopic consensus sessions, increase clinical-laboratory communication for unsatisfactory smears and cytohistologic discrepancies [1].

QA is the total process where the quality of laboratory reports can be guaranteed and encompasses procedures adopted for minimizing errors that may occur at any stage. High level of QA helps the treating physicians to arrive rapidly at a correct diagnosis. QA process is a managerial process of maintaining high standards of performance and of improving standards where necessary. Internal quality control is the process of minimizing analytical errors. Hence QC and QA are required to prevent, detect and correct errors [5].

Cervical cancer is commonest cancer in females especially in women of developing countries where 70% of cases are diagnosed at advanced stage. In a woman with two or more negative Pap smear, screening once in every 3-5 years and 10 years later yields an 80% and 64% reduction in the incidence of invasive cervical cancer respectively assuming 100% compliance. Screening once in 3-5 years at population level will prevent approximately 4 out of 5 cases of cervical cancer. Once in lifetime screening in women between 35-50 years of age causes 25-30% reduction in the incidence of cervical cancer. Organized screening programmes have greatest effect as in Finland, Iceland and England. Opportunistic and spontaneous screening is more common in USA and Canada. The mean sensitivity and mean specificity of cervical cytology is 58% and 69% respectively. The sensitivity and specificity reported in various studies by conventional smears is 30-87% and 86-100% respectively because of sampling

and detection errors. There is variation in outcome of the screening programmes due to false negative rates which is because of errors in screening and interpretation. High false negative rate is because of insufficient clinical information, poor smear quality, rare / small abnormal cells, expertise of the cytopathologist, etc. However, false negative rates are rarely measured in routine clinical practice. Hence QC and QA of cervical cytology reports are required for improving the performance of the test and eliminate false negative and also false positive results. False negative rate and false positive rate in cervical cytology tests reported are 2-55% and 10-54% (mean 35%) respectively. False negative reports are risk and more harmful for patients. False positive reports cause unnecessary surgical procedures and psychological impact to the patients [1,6,7,8].

The quality of gynecologic cytology was realized with series of articles published in the Wall Street Journal in 1987. Clinical Laboratory Improvement Amendments (CLIA'88) was passed in 1988 by United States (US) Congress which stated that coordinating laboratory activities regarding data collection, slide rescreening, correlation of cytology & histopathology findings, limitations of number of slides to be screened, proficiency testing and inter laboratory comparisons is a requirement for quality patient care. The College of American Pathologists (CAP) has initiated its role through Q-probes and Q-tracts programme to improve gynecologic cytology services with comparison of cytopathology laboratory internationally [9].

Actually the QA starts from the information or initiation at target population, labeling of samples, staining, cover slipping, interpretation and timely dispatch of reports including follow-up and treatment for patients with abnormal smears in early phase of the disease. QA at all levels of screening decreases the incidence up to 80% and avoids treatment of females with false positive reports [7,8]. Hence Pap test evaluation comprises several pre-examination, examination and post-examination steps as; knowledge regarding genital tract, biological variability, collection of samples (site and sampling method), identification of lesion, assessment of sample adequacy (quality indicator), laboratory procedure including processing, primary screening (manual / computer assisted), interpretation, timely dispatch of reports, preservation of slides / related documents and confidentiality of reports. Quality assurance regarding the interpretation of Pap smear includes various rescreening methods, participation in laboratory accreditation program which is voluntary participation (Eg: CAP: College of American Pathologists), peer review, inter laboratory comparison, education and procedural standardization. The quality indicators are relative percentage of unsatisfactory smear rate, percentage of abnormal smears above ASC-US (Atypical squamous cells of undetermined significance), ASC/SIL (Atypical squamous cells / Squamous intraepithelial lesion) ratio and cyto-histo correlation [1,5,10].

The QC is done by rescreening of all smears along with audit which determines the efficiency and effectiveness of routine cytological screening, but it is not feasible in high volume

cytopathology labs. Hence rapid rescreening of negative smears was considered and thought that it was feasible and was followed as QC procedure in UK. Rescreening detects false negative cases which are tool for quality control by comparing performance of different screeners which in turn monitors the performance of the lab over time. The strategy for the rescreening has to be defined before implementation as quality control programme regarding the various procedures, steps of the processes, feasibility, cost effectiveness, training of involved professionals and organized monitoring [1,6,7,8].

The dimensions of quality which help to achieve the QA are; equity & access (reaching the population having poorer assess), safety, efficiency and effectiveness. The information has to be protected, kept confidential and updated in cervical screening register [11]. Some of the procedures of quality improvement are; [1,7,10].

1. Verifying pre-analytical and analytical standards.
2. Uniform grading of abnormalities, the terminology of which is agreed at national level and comparable to The Bethesda System of reporting.
3. Internal quality assessment as; random re-screening of negative smears, rapid review, etc by well trained and qualified staffs. .
4. Cytovirological (Human PapillomVirus: HPV) co-relation to optimize screening accuracy.
5. External audit is critical by exchange of slides / digital images of selected cases.
6. Guided computerized screening improves the quality.
7. Cytology and corresponding histopathology co-relation.
8. Statistical monitoring.
9. Workload and time spent for each slide screening is essential to maintain the quality and acuracy of cytology reports.
10. Periodic training and certification of staff to update knowledge and skills is essential. In fact lifelong learning is essential for one to keep pace with the quality and update recent developments.
11. Proficiency tests are critical for continuous quality improvement (CQI).
12. The quality improvement tool should be PDCA cycle as “Plan, Do, Check and Act”.
13. Impact of the reports can be assessed by looking at the burden of the disease.

This write-up deals with the quality assurance of interpretation of the cervical smears

covering manual procedures, automation, internal QA and external QA.

2. Internal QA

The three elements of structure, process and outcome as proposed by Avedis Donabedian in 1988 can be applied to the cytology lab for the QA reports. The internal quality in cytology can be assessed by accuracy and reliability. The accuracy can be defined as the level of agreement between the diagnosis offered by the different laboratories and the gold standard is histopathology. It can be assessed by sensitivity, specificity, positive predictive value, negative predictive value, false positive rate and false negative rate which can be calculated for individual performers and for the laboratory. The reliability can be defined as the level of agreement between the repeated measurements of same cytological sample. It helps to know the inter and intra-observer's variability [1,4,12]. Following are the phases of internal QA in reporting of cervical cytology;

2.1. Request form

The request form should have complete details of the patient consisting of clinical details as presenting complaints, age of menarche, menstrual phase, history of any other cancer, family history of cancer, hormonal assessment, hormonal therapy, use of contraceptives, previous surgeries / chemotherapy / radiotherapy, previous reports of Pap smear, examination findings, etc. The information to the patient and consent is a requirement [7,13].

2.2. QA of Pap stain

Before screening, one should be satisfied with the quality of Pap stain of the smear. Each laboratory should develop the staining protocol for optimum staining of the smears. The internal quality indicator for Pap stain is the neutrophils, the cytoplasm of which takes greenish stain indicating that the smear is fixed and stained as per the protocol. The QA for Pap staining has to be checked daily with cervical or buccal smears and grading the staining pattern and intensity can be done. The parameters which can be checked are; intensity of nuclear staining, crispness of nuclear chromatin, contrast between eosinophilic and cyanophilic staining of the cytoplasm, quality of dehydration, clarity of mountant and use of appropriate thickness and length of cover-slip. The staining of gynecologic and non-gynecologic smears has to be done separately to prevent contamination. The quality of the stain of the slides can be checked randomly at yearly interval for fading of the stain. If stained well the intensity of stain persists for approximately three years [3,4,14].

2.3. Manual screening, pre-screening and re-screening of cervical smears

Documentation of all types of screening and reviews is required for QA monitoring. The laboratory should define the policy for re-screening and pre-screening as there are different

methods for re-screening [3]. The different methods are as follows;

2.3.1. Routine screening

Primary screening has to be done by the cytotechnologist / cytologist to avoid screening error. On an average 50 slides per day can be screened. A second level of check has to be done to prevent false negative rates. All positive or abnormal smears and borderline smears have to be seen by the qualified and experienced cytopathologist which is a daily internal quality control. A senior experienced cytopathologist should review the slide if the women has specific clinical features and clinical examination is suggestive of some abnormality as a daily internal quality control [4].

The smear has to be checked first for the adequacy which determines sensitivity and quality of report. The adequacy is determined by certain criteria as; the slide surface should be covered by more than 10% of the smear, more than 50% of the cells should be well preserved / well visualized and evaluable, smear should have junctional component in the form of 2 clusters of endocervical cells each having 5-6 cells each, slide should be properly labeled, the inflammatory cells / mucus should not cover more than 75% of squamous cells. If an abnormal cell is present in an inadequate smear, the smear has to be reported as adequate smear. This is a daily internal QC process [4].

Screening has to be done in “Meander” fashion with low magnification (X10 objective) for screening and high magnification (X40 objective) for the structural / nuclear resolution along with eye piece of 10X. The ideal screening time for cytotechnologist is 5 minutes for screening and one minute for documentation. Hence for quality reports in conventional smears, the total time required is 6 to 10 minutes per slide using 10X objective [3,4,8,11,15]. The recommended number of slides an individual can examine is 100 slides per 24 hours and not more than 8 hours (approximately 12.5 slides per hour)per day. However Pap smears reports depend on professional skill, concentration, posture, excessive / stressing workload, extreme pressure, etc which results in error reports, increases false negative reports and decreases the quality of the reports [3,15].

Different methods of screening the slides are used to overcome the false negative reports as; Whole technique, Turret techniques and Step technique (Figures 1,2,3) [15]. Turret technique was introduced by Baker e Melcher in 1991 and Step technique by Faraker in 1993. In Whole technique, most of the cells in the smear will be screened at fairly high speed. In Turret and Step method, the screening occurs at regular speed and therefore abnormal cells are likely to be detected in the path. However when all three methods are compared, Step method shows superior performance probably because of regularity of hand movement and constant velocity providing optimum conditions for the observer to trace the cells with subtle alterations. In Whole and Turret methods the speed is higher because of more simple hand movements giving

rise to higher velocity and higher rate of missed cases [15].

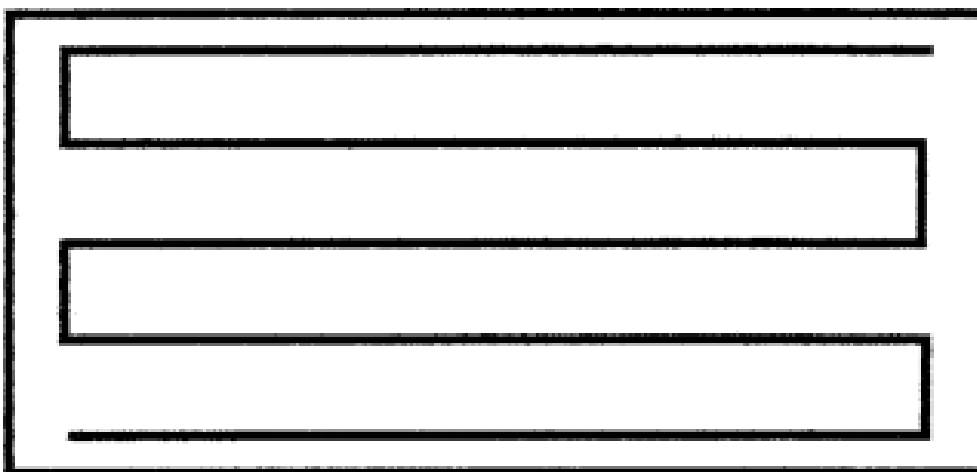


Figure 1: The whole technique: the observer reads the slide in horizontal direction



Figure 2. The turret technique: the observer runs the slide in horizontal and vertical (Greek bar) sense alternatively.

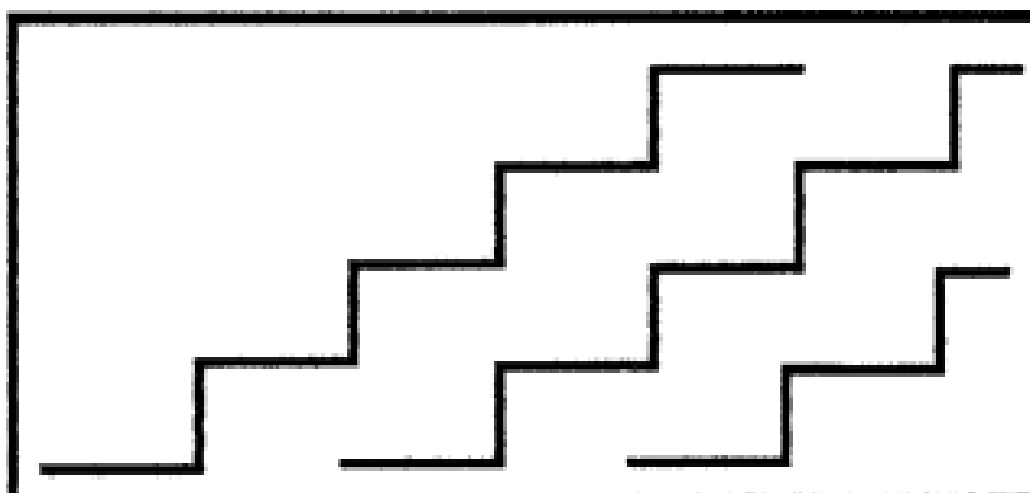


Figure 3. The step technique: the observer runs the slide in a stair-wise fashion.

The report should be in a descriptive nomenclature. The terminology used for reporting should be acceptable universally. Of all the types of abnormal cells, ASC-US is poorly reproducible, however experienced professional reproduce more accurately. The cytology report has to be correlated with HPV findings especially in case of ASC-US. Abnormal reports should be reported only by qualified cytopathologist. Monitoring and measuring the percentage of differ-

ent types of lesions (High grade, low grade, atypical, negative, inadequate and undetermined) by individual consultant and comparing with that of the other laboratory and the national standards also speaks of the quality of the report. Peer review and discussion of abnormal smears on daily basis among cytologists helps to harmonize the classification and keep up the quality of report. Before report dispatch one should match the request form and report form. The quality of reports in routine practice depends on false negative rates which define the efficiency and suitability of screening Pap smear. The sensitivity, specificity, false negative rate and false positive rate of reporting determine the quality of the report [3,4,11,15].

The percentage of lesions which are acceptable in the laboratory in a screening programme are; High grade squamous intraepithelial lesion (HSIL) which includes CIN 2 & CIN 3 (cervical intraepithelial neoplasia) is 1.6 +/- 0.4, low grade squamous intraepithelial lesion (LSIL) which includes HPV & CIN1, ASC-US and atypical glandular cells (AGC) is 5.5% +/- 1.5. For inadequate smear it is 7.0% +/- 2.0 [4].

2.3.2. 10% Random Rescreening (10% RR)

This is a method of choice in many laboratories for QA. Here 10% of all the negative or unsatisfactory smears are selected randomly and rescreened by full screening of the smears. This is the method followed in North America [6,9,16]. This method is recommended by IAC (International Accreditation committee) and CLIA 1998 [17]. The detection rate is 0.12% [6].

The advantages of this method are, it detects false negative cases and monitors staff performance levels. The disadvantages are, the selection of cases has no scientific basis, it is the ineffective means of detecting false negative cases as only a fraction of the negative smears are re-examined, hence sensitivity is low, difficult to monitor, screener knows that the smear has a prior negative diagnosis and may be biased, true measure of false negative rate cannot be measured and the method is ineffective to decrease the false negative rate and unlikely to detect with the statistical evidence the substandard quality of primary screener. The method has sensitivity of 30% and 0% for ASC-US & above and LSIL & above respectively. However overall increase in the sensitivity or performance of the lab cannot be done with this method [4,6,9,16,18,19].

The sensitivity to detect false negative smears by this method is 40.9% and specificity is 98.8% [15]. The false negative rate measured by this method is 5%-11%. It is one of the daily QC parameter for negative and inadequate smears [4].

2.3.3. Rapid Pre-screening (RPS)

This method is first described by Baker & Melcher and is an effective tool for QC. However it is not recommended by CLIA'88 and is not in practice in US. In this method all

Pap smears (negative for intraepithelial lesion and malignancy (NILM), unsatisfactory and abnormal smears) having 22x40 mm cover-slip are screened or pre-evaluated by rapid preview using 10X objective by “step screening” with the time period of 30-40 secs or 30-120 secs per slide with maximum of 40 slides. The “step method” described by Faraker approximately covers 20-25% of smear in screening of the slide. The size of each step in the diagnosed part of the pattern was about one microscope field by two. (Figures 4 & 5) 20% area under the coverslip is examined. The time interval between the slides should be 15 secs for documentation and changing the slide. The smears are screened before routine full screening. The pre-screening is ideally done in the morning and clinical information is not given to the screeners. Following RPS, the slides are subjected for routine full screening without revealing the information or markings over the slide. The intensity of RPS is equivalent to 1/6 of full slide screening and time devoted is 1/10 of full slide screening. The pre-screeners will not comment on the specimen adequacy. The sensitivity of this method is 35.8 to 81.4% and it increases as screeners gain experience and feed back on their performance. However HSIL is the most significant and reproducible for the purpose of the QC. The sensitivity RPS for HSIL and above, ASC-H and above and ASC-US and above is 65.4%, 20% and 29.4% respectively which mainly depends on the subjectivity in the diagnosis and longer observation of ASC cells. The sensitivity for infection is 48.6 to 87% and for that of endometrial cells is 28.3%. The false negative rate estimated by this method is 5.5%. Detection rate of RPS is 12.9%. It is ideal that the pre-screening is done by 2 individuals with variable experience and competence [6,9,12,18,20].

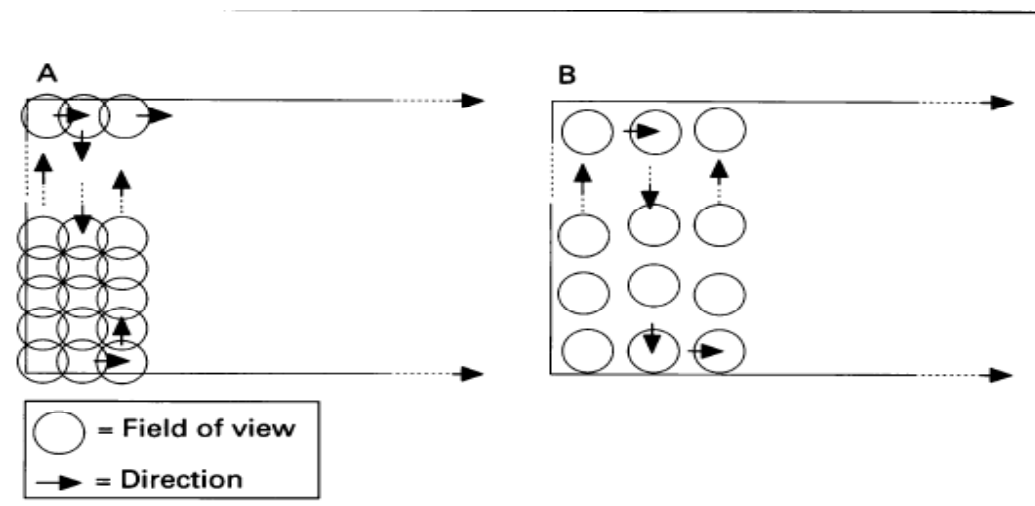


Figure 4: Diagrammatic representation of normal (A) and rapid (B) screening [16]

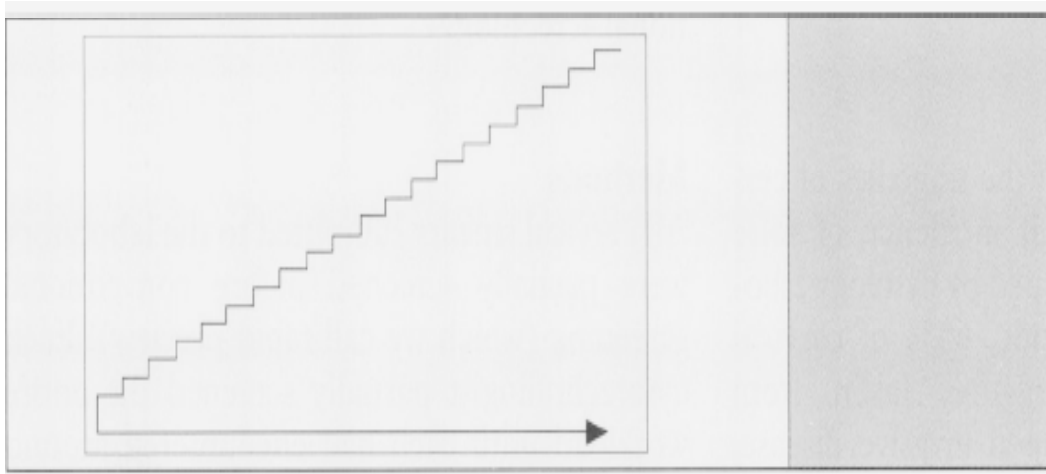


Figure 5: Screening pattern used in rapid review. Each step is approximately one field by two [12]

The advantages of this method are, this is a sensitive method as rapid review in detecting abnormal smears, possible to measure sensitivity because of subsequent full screening, additional cases are picked up on RPS, cost effective, better & accurate to estimate false negative rate, correction factor can be calculated, efficient than 10% random rescreening, can replace 10% random rescreening, twice as sensitive as 10% random rescreening, scope for correcting the diagnosis before the report is signed out, is ideal tool for QC in detection of SIL and improve patient care, detects approximately 27% errors in LSIL / HSIL cases, more effective in detecting HSIL, powerful QA method than ASC/SIL ratio, can be used for routine gynecologic rescreening, can estimate sensitivity, works in real life settings, it identifies 19 times as many errors, increase the performance of the lab, meaningful way to measure and improve the overall sensitivity of lab significantly. Two heads and four eyes are better than one head and two eyes, hence the advantage of RPS [6,9,12,18,20,21].

The disadvantages are, the method needs more paper work compared to 10% random rescreening, some consider it as review of individual performance, has low specificity, done in 100% (all) cases and hence time taken is twice as much as 10% random rescreening [6,9,12,18,20].

2.3.4. Rapid Rescreening (RR)

It was introduced in 1991 by Baker e Melcher [15]. The method is currently in use outside the United States (in use in UK). It is done by screening all the negative / inadequate smears using 10X objective covering much of the slide in 30 seconds to 2 minutes in normal pattern but bigger steps approximately covering 35 fields per slide. Some of the studies have used different screening pattern. The time spent for each field is usual. It should be done as the first task of the daily schedule before commencing routine screening and the suspected cases are studied later for a final diagnosis. It is ideal to use the timer for start and stop at 30 seconds interval. The screening is done without the knowledge of clinical details. It is recommended that a cytologist or cytotechnologist should not review more than 20 smears at a time i.e., 30

minutes [4,9,16,18,19].

Inexpensive, cost effective, effective method, alternative to 10% random re-screening, less time taken, more productive in finding errors than 10% random re-screening, detect high proportion of abnormal smears in a limited scanning time, more effective in detecting HSIL, effective method of daily internal QC for negative and inadequate smears, detects greater numbers of cases of missed high grade dyskaryosis than any of the other methods with respect to the allocation of lab resources as at times high grade cells are small and pale, provides valuable data, identifies poor primary screener or performer, individual false negative rates can be calculated which are guide for screeners to gain confidence and be competent, educational, less human resources, high detection of false negatives rates [4,6,9,16,19,21]. It is considered as superior to 10% RR and practiced in Europe and Australia [6].

The disadvantages of this method are; it does not prevent false negative results in the report as the procedure is done after the dispatch of reports [16]. The screener is aware of the previous interpretation of the slide, not a method to monitor sensitivity and effectiveness. RR of selected cases with deliberate inclusion of abnormal cases was proposed, but difficult to apply and not reproducible in real life situations [6]. The sensitivity to detect false negative smears by this method is 73.5% and specificity is 98.6% [15].

2.3.5. 100% Rapid Rescreening (100% RR)

Here all the cases (100%) are re-screened which includes negative smears, unsatisfactory smears and abnormal smears. The procedure of screening, advantages and disadvantages are similar to RR. However in addition to detection of false negative rate, the upgrading and down grading of the diagnosis can be made. Hence it is a better quality control tool and helps in identifying the poor performers [9,19].

2.3.6. Double screening

In this method the laboratory makes the policy that each smear has to be screened by at least two cytopathologist or cytotechnologist where two heads and four eyes will be contributing and finalizing the report. It is most effective and sensitive method. It is the method of choice if it were not so time consuming and expensive [16].

2.3.7. Partial re-screening

Here all negative and unsatisfactory smears are subjected to quick review (30-120 seconds) after conventional screening but prior to issue of the report [16].

2.3.8. Re-screening with Clinical Risk Criteria (RCRC)

In this method the smears are re-screened only in patients of high risk group. The high

risk group is one with clinical findings as post-menopausal bleeding, contact ectocervical bleeding, sexually transmitted disease, abnormal per-vaginal, per-speculum or colposcopic findings and previous radiotherapy. Here negative and unsatisfactory smears are re-screened which are more likely to have errors. The advantage of this method is, one can identify higher rate of errors and has higher sensitivity compared to 10% random review. However like 10% random review false negative rate cannot be measured [18].

2.3.9. Clinically indicated double screening

In this method some of the smears which are clinically indicated undergo double re-screening as the clinical suspicion of abnormality is quite high. The smears are screened in detail by taking 5 to 6 minutes per slide. The rate of detection of false negative is 5.3% [16]. The discordance in interpretations can be utilized for continual education. Peer review can be considered for the QA. An outside consultant can be considered for unusually difficult cases having significant clinical implication [18].

2.3.10. Targeted re-screening

Here the smears of previously detected abnormal or symptomatic cases are re-screened by taking 5 to 6 minutes per slide. The method mainly aims at follow-up of cases especially in young women. However it has limited contribution to decrease false negative rate in future [12]. The detection rate is 15% [6].

2.3.11. Retrospective re-screening

It is the targeted re-screening done in the smears of patients preferably of past 5 years diagnosed as negative for intraepithelial lesion or benign cellular changes with current significant abnormality as SIL or carcinoma. Such cases have to be identified, discussed and looked whether it is a false negative case. This is a periodic internal QC. According to CLIA '88 it is recommended in US. The screening is applied to only selected and high risk patient smears. The case records of such cases should be labeled as "confidential, for internal QA use only" and kept separately. It is an internal quality record. The amended report is given only when current patient care is affected by a discrepancy noted on re-screening [3,4,6,8,9].

The disadvantages are, the error rate detected is not a measure of overall screening performance. The procedure does not reflect current screening performance. It is only error detection. The re-screening result is of not much use currently to the patient. Increased re-screening error yield per case is lower [4]. This method of review is subjected to biasing effect of the knowledge of clinical outcome [3,4].

The advantages are, it is of great educational benefit, internal quality record and corrective action can be taken by the reporting staff for future benefit and sometimes for patient care.

Benefit of re-screening is more with current LSIL, as LSIL cases are almost 3 times as HSIL [3,4,9].

2.3.12. Real- time re-screening

It is the rescreening of the current smears consisting of risk cases as well as 10% random rescreening by a second screener prior to reporting. According to CLIA '88 it is recommended in US [9].

The advantages are, it is a long standing quality monitor in the cytology lab. According to various studies, rescreening by this method in risk cases has identified 40 times the number of errors of which 70% were ASC-US and AGC compared to random rescreening. It helps to find out false negative cases, extrapolating to the entire population screened and useful as internal performance monitor. The other advantages are error detection that directly benefits the current patients, pattern of performers, identify systematic problems at the earliest opportunity and more useful ongoing competency assessment [9,16].

The disadvantages are, it takes long time for adequate number of randomly selected cases to get statistically valid comparison and calculation. If ASC-US is used as threshold to calculate errors, there will be more cases with errors and false negatives as ASC-US is less reproducible. Therefore it is not advisable for inter-laboratory comparison. If SIL is used as threshold to calculate errors, it takes long time to accumulate the error information and identify poor screening performance. However it is appropriate for inter-laboratory comparison [6,16].

2.3.13. Seeding abnormal smears in cytology workload

In this method abnormal slide or known positive slide is seeded to routine screening. This method helps to increase the concentration of cytoscreeners and identify the unsatisfactory performers. The results depend on whether the cytoscreeners are aware of the screening method. It is suggested that this method can be used occasionally and not systematically to assess the cytoscreeners [4].

2.3.14. Follow-up of patients with abnormal cytology results

It reflects provision for basic patient care and timely follow-up evaluation in women with abnormal smears (sentinel events) as described by National Committee for QA. However it does not evaluate laboratory performance. The positive cases can be reviewed for the risk factors and the frequency of Pap smear screening. It helps to take preventive steps and can access the interval period between the negative and positive smear [4,9].

2.4. Personnel involved in screening the Pap smear

The personnel screening the Pap test determine the quality of the reports of cervical cytology. The personnel involved should be qualified and experienced Pathologists, cytoscreener, cytotechnologists and cytotechnicians. Cytoscreeners should have bachelor degree in laboratory technology and 2 years training in any referral center to screen Pap smears. Cytotechnologists should have passed Indian Academy of Cytology certification exam. Cytotechnicians should have undergone one month training in cytology lab in tertiary referral center for staining Pap smears. Routinely 10% random rescreening of Pap smears by Pathologists which are already screened by cytotechnicians or cytotechnologists and correlating it with histopathological reports (Reported by two Pathologists) are followed in many labs [18]. The reproducibility of results improved with increased training of staffs as high reproducibility increased sensitivity and specificity of reports [8,22]. The reporting staffs should have training programmes, certification and continual professional education for competence of screening [4].

2.5. Screening limits and competency assessment

Individual screener workload limits should be based on the competency assessment of the personnel and it has to be monitored every six months with laboratory defined performance standards. As per CLIA 1988, the maximum number of slides which can be screened by cytotechnologist is 100 slides per work day independent of other duties of screening personnel. Increased error was identified by rescreening previously diagnosed negative smears in cervical cytology with increased expectation of cytotechnologist productivity [3,9]. As per the European Federation of Cytology Society, the work load of cytotechnologist maintaining the diagnostic skill should be minimum of 3500 smears and not exceed 7000 smears per annum [4]. Some of the limitations of screening is lack of concentration, screening fatigue, misinterpretation, not readily recognized as dysplastic cells, scanty cellularity and microbiopsies [12].

Bias is a significant limitation in rescreening. It can be over interpretation or under interpretation biases. The over interpretation bias in legal settings is well known and it is the reason for the development of guidelines for review in legal settings. However it is difficult to eliminate bias including distraction factors. It can be reduced only by multiple blinded slide rescreening especially in legal settings and implementing standard reporting format to measure errors as false negative rate, false negative fraction and false negative proportion. However there is no exact method to measure errors and rectify bias [23].

The limitations of rescreening also depends on the biological variability as; failure of exfoliation of malignant cells especially in post-menopausal women resulting in false negative cases, necrosis or hemorrhage of tumour tissue resulting in unsatisfactory smear, cellular alteration due to hormone related changes, drying artifact in smears of post-menopausal women,

reactive changes in immature metaplastic cells and sampling errors. The smears are better diagnosed in women between 35-64 years of age than those of less than 20 years of age [24].

All reporting Pathologists should actively take part in continual professional development (CPD) programmes, in recognized cervical cytopathology external quality assurance (EQA) schemes and clinico-pathological correlation (CPC) meetings to improve the competency. To maintain the diagnostic skill of cytopathologist, a minimum of 750 slides per annum has to be screened. The cytology manager or supervisory scientific staff should screen at least 750-3000 slides per annum depending on the role. The continuing education is a requirement which includes regular or scheduled internal and external education. Internal education includes discussion of difficult or review cases and also updates the information. External education includes attending workshops, inter-laboratory slide review, proficiency testing, teaching students or technicians, writing books related to cytology and community outreach programmes. Proficiency testing is mandatory for CLIA 1988 [3,11].

The cytopathologist or cytotechnologist can be given assessment and educational slides for interpretation in the normal working environment and their skills can be assessed at regular intervals. All the participants will receive personal and comparative results. The individual performance has to be kept confidential. The persistent poor or substandard performers as per the standards and also staffs after long leave have to be refrained from regular reporting and for such individuals supportive, constructive in-house or off-site training has to be given. The educational slides should be challenging and interesting which should be for discussion and teaching for continued professional development (CPD). Annually the certificate of participation can be given. The annual performance including performance indicators and activity analysis has to be maintained [24].

2.6. Examination of unknown slides (Survey program)

It is a method to assess and compare screening and diagnostic performance between labs organized by reputed organizations. It is not the routine screening activity of the lab. CLIA 1998 organize glass slide proficiency testing for labs performing gynecologic cytology. CAP organize inter laboratory glass slide program. It is an interlaboratory comparison program in cervico-vaginal cytology and is a quarterly glass slide program where graded and education sets are used since 1996 and separate answer sheets are used for Pathologists and cytotechnologists. The individual response can be used as competency test. The discrepancy rate reported is 4%. The error rate is 1-2% higher for new Pathologists and hence it is of educational value. The error rates are reported to be higher in labs with a small gynecologic cytology care volume with only Pathologists and no cytotechnologists. In Pap 1998, the lab concordant response reported for LSIL, HSIL and SCC were 94.2%, 97.8% and 98.7% respectively [9].

2.7. Turn around Time (TAT)

The turnaround time is one of the quality indicators and provides an opportunity for improvement. The turnaround time reported in literature for gynecologic cytology is 6-8 days. Quality of evaluation is the priority in cytopathology labs. High quality evaluation and acceptable turnaround time are not necessarily mutually exclusive. Some time the turnaround time is longer during weekends. Hence turnaround time has to be defined for timely report dispatch. The turnaround time can be prolonged due to insufficient clinical information for optimal processing of cytology slide where redesigning of the requisition form and regular interaction with clinicians is required. Some specimens need short turnaround time as symptomatic patients who require priority and rapid processing [6,18].

2.8. ASC / SIL Ratio

It is the ratio between the atypical cells and cells with intraepithelial lesion in cervical cytology. It is one of the quality indicators in cervical cytology. The accepted value of ASC is approximately 5% of all Pap tests. However ASC increases with increased screening in high risk population. ASC/SIL ratio is less dependent on the patient population as high risk population has increased values of both ASC and SIL. Hence ASC/SIL ratio is a better quality indicator than only ASC value which can be used as a measure of QC and QA. It is a surrogate marker to assess the level of certainty (Specificity and sensitivity). It is ideal to maintain ASC/SIL ratio of less than 2:1 or 3:1. Kurman and Soloman have stated that the ASC / SIL ratio should be 2 or 3. The CAP lab accreditation program has recommended the acceptable ratio between 0.4 to 5.1 using 5th and 95th percentile limits [9,20,21].

The ASC/SIL ratio can be calculated for the individual cytopathologist and also for entire lab but not much for cytotechnologists. However the ratio for cytotechnologist in some labs is kept greater than 1.5 to ensure adequate screening sensitivity, as significant reduction of ASC sacrifices the sensitivity. In gynecologic cytology, the cytotechnologists maintain adequate sensitivity and cytopathologists maintain adequate specificity by downgrading the smears as negative and improve specificity. Hence ASC/SIL ratio should be less in cytopathologist compared to cytotechnologists. The ASC/SIL ratios not effected by volume of slides, workload, slides images, non-images or preparation type [20,21].

2.9. Cytology HPV Testing Correlation

HPV testing is done mainly to look for positivity of high risk HPV (HR-HPV) in ASC-US which helps in further recommendation as; if HPV negative, the patient will be screened as routine protocol (once in five years or can be extended to ten years) and if positive, annual screening is recommended till negative. Hence the HPV testing should have quality requirements and standards to ensure the accurate and reliable reports. HPV testing was introduced

in cervical screening programme in 2012. HPV testing is also included in ASC-US triage. The test is done using the sample taken for liquid based cytology after processing for the cytology smear. The testing method should be standardized and FDA approved for quality care [11,25].

As per the second edition of European guidelines for quality assurance in cervical cancer screening, primary HPV-HR testing fulfills the evidence based and QA of cervical cancer screening compared to only cytology based screening. HPV testing is ideally done between 30 to 60 years of age [25].

2.10. Cytology Biopsy Correlation

This is a requirement for CLIA 1998 for QA where the internal QC is done periodically. The histopathologic diagnosis correlation is considered as gold standard on internationally accepted terminology. The cytologic assessment can be done by conventional method or newer methods as liquid based cytology or automated screening devices [21]. It will evaluate performance of cytology lab and in fact failure to correlate indicates problems in cytological diagnosis, histopathological diagnosis or clinical sampling. In case of non-correlation, cytology and histopathology slides have to be reviewed and discussed for consensus which helps to formulate criteria for patient selection, samplings methods and re-education of the individuals. The level of agreement is a measure of lab quality. It is ideal to have a narrow time frame between the cytology and biopsy sample from the same site in a given patient. The findings are to be correlated and a cumulative quarterly report has to be made and then compared to the bench mark for improvement. The positive predictive value of the cytology report should not be less than 65%. The positive predictive values are usually higher in hysterectomy specimens and cone biopsy than punch biopsy. The correlation depends on the expertise of colposcopist and quality of biopsy [4,7,8,9,26].

Discrepancy rate is defined as the proportion of cases with interpretative cytologic or histologic errors during the period examined. The cyto-histo discrepancy is defined as a two steps or greater difference between a cytologic and histologic diagnosis made on the patient within a six month period. For gynecologic cytology, atypical squamous cells and atypical glandular cells are to be excluded from the analysis [9,26]. The discrepancy is because of errors which can be graded as reactive, atypical and malignant. The estimation of individual pathologist discrepancy rate, specimen type discrepancy rate and inter-observer diagnostic variability has effect on patient outcome as additional procedure, delay in diagnosis, morbidity and mortality. However if the discrepancy is minor, it goes unnoticed [26]. The average interlaboratory discrepancy rate is 5% [27].

The sampling or interpretative errors can give rise to under calls or overcalls in cytology or histopathological diagnosis. Under calls is the disparity between original diagnosis and

review diagnosis where the original diagnosis was less severe than review diagnosis by one step or more. In overall the original diagnosis will be one step more severe than the review diagnosis. In gynecologic cytology, majority of the discrepancies are due to interpretative error than sampling error unlike non-gynecologic cytology. Comparing cytology and histologic misinterpretation, it is more histologic error than cytology because of greater variation in thresholds for diagnosing cervical dysplasia. Usually the difficult cases are more prone to error [26].

The cytology biopsy correlation encourages new sampling technique and automated screening for improvement in cytology reports. In UK screening program, the range for biopsy proven HSIL following an HSIL cytology diagnosis has been set from 65% to 85%, similar to Q-probes study. In Q-probes study, 63% of ASC-US and 52% of AGC showed intraepithelial lesion or malignancy in biopsy [9].

The advantages are; it provides opportunity to improve, represents performance of all personnel in both labs, quantify the quality of performance, evaluates at each step for improvement, is an internal lab review process which facilitates interaction with clinicians and resolves the problem, improves the delivery of cancer prevention services, efficient patient care, less unnecessary procedures, is quality indicator in the gynecologic cytology lab, enhances continuous quality improvement program & interpretative skills, educational measure, helps in refining diagnostic criteria, accuracy and reproducibility [3,9,26].

The cervical cytology should also be compared with findings of colposcopy at the time of taking biopsy [28]. The cytology histology policy has to be documented for QA. If biopsy is not available, the laboratory should attempt for follow-up material or patient information [3].

3. Newer Technologies in QA of Cervical Cytology

3.1. Liquid based cytology (LBC):

The type of smear preparation also matters for quality reports as, inadequacy are common in conventional smears. Liquid based cytology smears show thin layer of distribution of cells, increased adequacy, well preserved glandular representation, increased detection rate of SIL, decreased ASC/SIL ratio, low unsatisfactory rates, less time for interpretation, ancillary test as HPV-HR DNA can be done in the same sample, decreased recalls (less expenditure) and can introduce slide reading automation. However the cost is more compared to conventional test. The shelf life of vials used in this method is a quality indicator. The shelf life of vials used in Thin-Prep is 2 years and 6 weeks in virgin and patient collected samples at room temperature respectively. The shelf life of vials used in Sure-Path is 3 years, 4 weeks and 6 months in virgin and in patient collected samples at room temperature and at -17 to -13 degree centigrade respectively. There is short expiration interval after sample collection. However HPV-DNA

detection by Hybrid Capture 2 method is not affected. The LBC has separate QA monitors compared to conventional method [7,9,21]. The staff using LBC should be trained for quality reports [3].

3.2. Computer assisted technologies:

This can be also used for automated pre and post-screening procedures. These are not feasible in developing and resource limited countries [15]. Some of these techniques are;

3.2.1. Imaging systems

The imaging systems are used in cervical cytology for quality assurance especially for retrospective rescreening to detect effectively the imaging, human locator and human interpretative errors. Imaging errors is one where the atypical cells are not present in the focus of vision (fov). In human locator errors, the cells are present in the focus of vision but are not recognized and marked as significant by the cytotechnologist. The human interpretative error is one where a typical cells are present at the focus of vision, recognized and marked, but interpreted as not significant. Hence imaging systems determine the abnormal cells in fov and also interfaces between the human and instruments that are most prone to error [9,21].

3.2.2. Automated prescreening and rescreening instruments

Here the computer analyses the digital images for identification of premalignant or malignant cells. One of the devices is approved by FDA which can be used for screening as well as for re-screening mode. The advantage of this instrument is, it decreases false negative rates and increases the sensitivity of screening [3,9].

3.2.3. Microscope process control system

This assists in QC and QA of reporting cervical cytology. It gives the direction, mode and speed of screening automatically. The advantage is, it monitors the speed, marks the area of interest, relocates the cells for review, screens whole smear, helps in final interpretation and also this is available in real time for generation of statistical data required for QC and QA [3].

3.2.4. AUTOPAP

It is a non-interactive automated system which can be used both for primary screening and review of negative slides. The instrument examines conventional slides and gives cellular atypia score based on mathematical algorithms. The level of grading considering the number of abnormal cells depends on the operator. However 10% random rescreening is not required as instrument enhances case selection by slide screening system. It is FDA approved where normal and NILM slides not require rescreening (25 to 50% of smears). However validation

of instruments and control check of positive and negative smears are recommended. It can be used to rescreen the negative slide by primary screener as internal QC [4,9].

3.2.5. PAPNET automation screening system

This is a FDA approved system used for rescreening of smears after conventional screening which serves as internal QC. However time required is double than that of rapid rescreening and is expensive [6,12]. It has two functions; Scanning and reviewing. In scanning function, the system captures two sets of 64 images in each cervical smear. In review function, the images are reviewed by cytotechnologist and cytopathologist and classify as negative images. The negative image reports will be dispatched and the review image slides will be screened in the microscope for abnormal cells. However this system has left the market in 1999 [4].

The work load, the time of the day and the day of the week determines the detection rate and quality of cytology reports in newer technologies. The quality deteriorates during 2nd half of the day [21]. For the Thin Prep imaging, the FDA has approved a maximum screening volume of 200 slides in 24 hours that are not to be screened in less than an eight hour work day. There are no national or federal guidelines for number of Thin Prep imaging system slides which should receive full manual review if reported as negative on initial FOV review. However CLIA makes mandatory that 10% prospective re-screening is required for negative smears [21].

FDA has given pre-marketed approval for BD focal point GS imaging systems, an automated, guided imaging system that screens conventional Pap smears and BD Sure Path Pap tests for an individual cytotechnologist to use the device to screen no more than 170 slides in 24 hours. As per the CLIA requirement for slides having material covering less than half of slide surface, cytotechnologist have to restrict to 200 Sure Path slides in 24 hours and should screen in no less than 8 hours. On an average, 8.9 slides will be screened per hour. The FDA has given pre-marketed approval for the focal point GS imaging system to allow 25% of images in conventional and Sure Path slides to be released as normal without further human review and out of remaining 75%, at least 15% slides should receive full manual review for quality control [21].

4. Measuring Error Rates & Error Detection

Method of measuring error rates vary and utility of these also vary. The ultimate aim should be to decrease error rate. The patient safety and outcome measures the impact of errors. The gold standard to measure error rates in gynecologic cytology is cyto-histo correlation and clinical follow-up in some instances which was mandated by CLIA 1988. However in gynecology cytology, rarely biopsy is obtained for correlation. Hence the reproducibility i.e, reviewing material for the 2nd time is considered as gold standard. The reviewing is done for

every case or if random, no selection bias should be used. Reproducibility however is not an independent gold standard method, measures precision than accuracy and it is a legal system to measure error. Reproducibility is poor for ASC and AGC, and many times no consensus reached in national educational and proficiency tests in which case field validation is an accepted method [23].

All discrepancies are not equal to error. Consensus should be done between the reviewers. Results of multiple reviewers have to be considered and correlated to achieve the truth and majority opinion is accepted as truth. Multiple blinded reviews are considered in legal settings and litigations to distinguish between disagreement and errors and decrease bias [23].

There should be some standard method to report errors which can be compared. In gynecologic cytology, it is in terms of abnormality rate. Average error rate reported in gynecologic cytology is at least 20%. Blinded crossover method is used to detect and measure error in terms of the abnormality rate. Reproducible diagnosis with truth and reduced bias defines error. Usually false negative rate for labs and individuals is approximately 20% for routine screening at level of ASC and LSIL [23].

Error rate is reported in terms where all cases are reviewed and has been called abnormal by at least one prior observer. However all abnormal gynecologic smears are not reproducible. Error rate can be decreased by monolayer techniques and automated screening devices. Reviews of cases are likely to have errors than review of random samples which defines accurate error rate [23].

5. External Quality Assurance System

In UK first histopathology EQAS was done in 1990 for NHS breast screening programme (BSP) in largest scheme. The NHS BSP later in 2005 implemented action plan for pathologist who fail to meet the minimum standards. EQAS is implemented in cytology and also in cervical cytology. EQAS improves consistency of diagnosis, quality of prognostic information with national standards, consistency of the reports throughout the country, monitors performance, assures high quality service, provides education value encouraging feedback on their performance, identifies persistence poor performers and is resource intensive. In future it may become compulsory. However the limitations of EQAS are; has to develop robust scoring system, time consuming, poor performers may be shown as in competent persons and vice versa, validity of EQAS is done as good or poor performers, diagnosis on digital images does not reflect the routine work (not mirror real life), not assess approximate hardware, not reflect current practice and hence sometimes not considered valid [4,13,23,24].

The methods of EQAS are exchange of slides between laboratories, proficiency testing, accreditation and certification [4].

In exchange of slides scheme, the smears having relevant histopathological reports are exchanged between the laboratories for consistency of diagnosis. The programme has to be organized, with different set of slides, structured report format, done within specific time, diagnosis to be given later, discordant reports should be discussed and the lab results should be confidential unless particular lab has to be intimated to improve the performance [4].

In proficiency testing scheme, the performance is assessed by unbiased external independent assessor. The facilitator gives a set of ten slides which has to be screened in two hours. The results are assessed for individual participant or for the particular laboratory which can be compared with other anonymous laboratory [4].

Accreditation is the autonomous organization committed to improve the quality of care to the patients, safe environment for the laboratory personnel, quality management system and certification for system of quality. There are many accreditation bodies. For the laboratories in India, NABL (National Accreditation Board for testing and calibration Laboratory) is the accreditation body which performs as per policy of International Organization for standards (ISO). The certification has to be renewed at fixed intervals following external audit. ISO is a worldwide, non-governmental federation of national standards bodies from more than 140 countries for setting future universal quality standards. The lab will be conducting at regular intervals the internal and external audit to maintain the standards and quality of the lab. The accreditation is of two types; Institutional or operational accreditation and professional or quality accreditation or accreditation of excellence [1,4]. The accreditation can be considered for the cytology laboratories to give quality cervical cytology reports and get NABL accreditation where the QA is based on the standards published guidelines. This external accreditation is renewed once in two years [3,4,22,28,29].

The laboratory should follow PDCA (Plan, Do, Check and Act) phases of Deming's wheel for total quality, achieve the defined standards and CQI (Figure 6) [4].

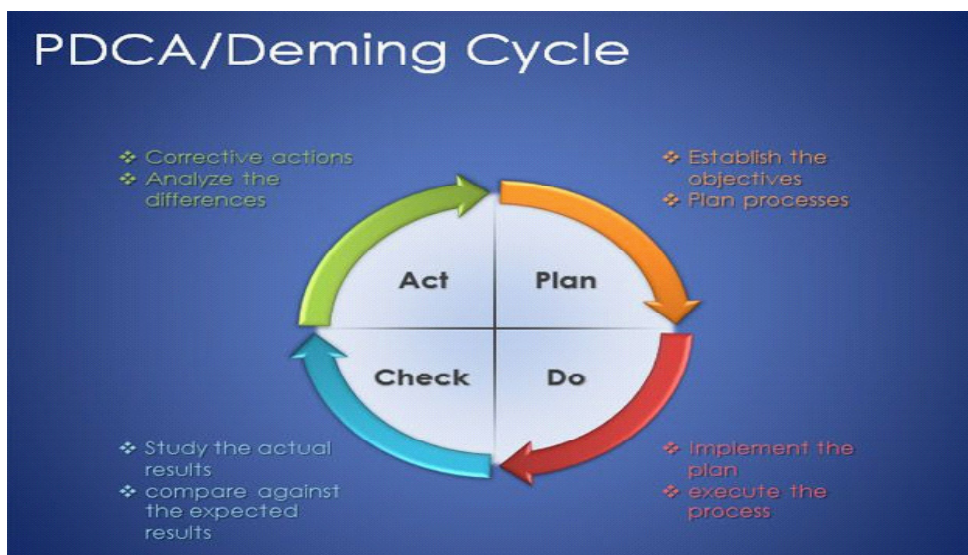


Figure 6: Shows PDCA / Deming cycle [30]

6. Diagnostic Statistics

Statistical summary with graphs of the diagnosis should be done in cytopathology labs dealing with cervical cytology at regular intervals and observe for any gross changes. Ideally the summary has to be done for every three months in gynecologic cytology labs with 10,000 to 60,000 cases per year. The statistics can be affected by the introduction of the liquid based cytology. Each cytotechnologist should have their own statistics for abnormal diagnosis which has to be compared with laboratory statistics. The reporting Pathologists should also have their statistical analysis which reflects their performance especially when there is high percentage of report of a particular diagnosis in which case peer audit of selective diagnosis can be done to improve the laboratory performance. For diagnosis of dysplasia or malignancy, especially HSIL and to some extent LSIL, an opinion of a second senior experienced Pathologist can be considered by which criteria for the diagnosis can be established. Statistical analysis of ASC / SIL ratio has to be monitored and opinion of peer review has to be considered in case of high ratio to explain the reason [9].

7. Conclusion

Quality assurance is a requirement for cervical cytology reports which has to be done by regular longitudinal monitoring and inter-laboratory comparisons. One should take care of procedure of sampling and processing of conventional or liquid based cytology for quality screening, judicious interpretation and quality reports (Figure 7). Conventional smears are cost effective. However liquid based cytology along with newer technology provides additional opportunities and challenge to improve detection of abnormal smear.

Regular internal audit should be the priority. External audit reassures the QC and QA. The laboratory should make the protocol and monitor daily and periodical quality indicators for internal quality (Figures 7, 8 & 9) [4]. Continuous education programmes of the laboratory staffs enhance the QA. QA in cervical cytology reduce risk of errors, set & reset standards, help professionals & organizations improve their performance and identify & manage errors effectively & sensitively. QA in screening also aims balancing between false positive and false negative rates for the quality and effectiveness of screening programme.



Figure 7: Flow diagram of quality control check of negative and inadequate smears after primary screening [4]

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: <ul style="list-style-type: none"> • HSIL (CIN2 and CIN3) • LSIL (CIN1 and HPV) and ASCUS and AGUS • Inadequate 	1.6% ± 0.4 5.5% ± 1.5 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

Figure 8: Quality standards in cervical screening (NHSCSP) regarding technical process showing indicators and threshold [4]

<p>1. <u>Internal quality control procedures</u></p> <p>On a daily basis</p> <ul style="list-style-type: none"> • 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: <ul style="list-style-type: none"> ➤ Random rescreening 10% ➤ Rapid review 100% ➤ Automated systems 100% • Peer review and discussion of abnormal smears • QA Procedures at the reporting phase <p>Periodical (not applied on a daily basis)</p> <ul style="list-style-type: none"> • 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
<p>1. <u>External quality control procedures</u></p> <ul style="list-style-type: none"> • Exchange of slides scheme • Proficiency Testing Schemes • Accreditation and certification
<p><u>3. Other important measures that assure the quality of cervical screening</u></p> <ul style="list-style-type: none"> • Training, certification and continuing professional

Figure 9: Showing Quality control procedures in reporting cervical cytology [4].

8. References

1. Branca M, Longatto-Filho A. Recommendations on Quality Control and Quality Assurance in Cervical Cytology. Acta Cytologica 2015; 59: 361–369.
2. Branca M, Longatto-Filho A. Recommendations on Quality Control and Quality Assurance in Cervical Cytology. Acta Cytologica 2015; 59: 361–369.
3. Quality Control and Quality Assurance Practice. In: American Society of Cytopathology, Cervical Cytology Practice Guidelines. 2000. p21-25.
4. Branca M, Coleman DV, Marsan C, Morosini P. Quality assurance and continuous Quality Improvement in Laboratories which undertake Cervical cytology. Pharma IT Srl 00196 Roma – Italy.
5. Guidelines for good clinical laboratory practices (GCLP). Director – General, Indian Council of Medical Research 2008; 18-22.

6. Djemli A, Khetani K, Auger M. Rapid Prescreening of Papanicolaou Smears; A Practical and Efficient Quality Control Strategy. *Cancer (Cancer Cytopathol)* 2006;108:21–6.
7. Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, Wiener H, Herbert A, Karsa LV. European Guidelines for Quality Assurance in Cervical Cancer Screening. Second Edition—Summary Document. *Annals of Oncology* 21: 448–458, 2010.
8. Methods for Screening and Diagnosis. In: European guidelines for quality assurance in cervical cancer screening. 2nd Edition. International agency for Research on Cancer. Eds: Arbyn M, Anttila A, Jordan J, Ronco G, Schenck U, Segnan N, Wiener HG, Herbert A, Daniel J, Von Karsa LV. European Cancer Network (ECN) Coordination Office, International Agency for Research on Cancer, Lyon, France. 2008; p69-152.
9. Bruce A. Jones, MD; Diane D. Davey, Quality Management in Gynecologic Cytology Using Interlaboratory Comparison. *Arch Pathol Lab Med.* 2000;124:672–681.
10. Suneeta K, Emily M, Deborah P, Beena V. Advancing cervical cancer prevention in india: implementation Science priorities. *Theoncologist* 2013;18:1285–1297
11. Quality assurance in cytopathology. In: Eds; Kelly S, Davin-Power M, Downey P, Flannelly G, Freeman-Wang T, Gleeson J, et al. Guidelines for Quality Assurance in Cervical Screening. National Cancer Screening Services. 2nd Edition. p48-66.
12. Faraker CA, Boxer ME. Rapid review (partial rescreening) of cervical cytology. Four years experience and quality assurance implications. *J Clin Pathol* 1996;49:587-591.
13. Parham DM. External quality assessment slide schemes: pathologists' experiences and perceptions. *J Clin Pathol* 2006; 59: 530–532.
14. Kalyani Raju. Evolution of Pap stain. *Biomedical Research and Therapy* 2016; 3(2): 490-500.
15. Montemor EBL, Roteli-Martins CM, Zeferino LC, Amaral RG, Fonsechi-Carvasan GA, Shirata NK, Utagawa ML, Longatto-Filho A, Syrjanen KJ. Whole, Turret and step methods of rapid rescreening: Is there any difference in performance? *Diagnostic Cytopathology* 2007; 35(1): 57-60.
16. Baker A, Melcher D, Smith R. Role of re-screening of cervical smears in internal quality control. *J Clin Pathol* 1995; 48: 1002-1004
17. Establishment of Cytology services at District hospital. In: Guidelines for cervical cancer screening programmes. Government of India – World Health Organization collaborative programme (2004-2005). Department of Cytology and Gynecological Pathology, Postgraduate Institute of Medical Education and Research, Chandigarh, India. 2006; p25.
18. Tavares SBN, de Sousa NLA, Manrique EJC, de Albuquerque ZBP, Zeferino LC, Amaral RG. Comparison of the Performance of Rapid Prescreening, 10% Random Review, and Clinical Risk Criteria as Methods of Internal Quality Control in Cervical Cytopathology. *Cancer (Cancer Cytopathol)* 2008; 114:165–70.
19. Sood N, Singh V. Evaluation of 100% rapid rescreening of cervical smears. *Indian J Pathol Microbiol* 2009; 52(4): 495-97.
20. Renshaw AA, Deschênes M, Auger M. ASC/SIL Ratio for Cytotechnologists A Surrogate Marker of Screening Sensitivity. *Am J Clin Pathol* 2009;131:776-781.
21. Crothers BA, Darragh TM, Tambouret RH, Nayar R, Guliz A, Barkan GA, Zhao C, Booth CN, Padmanabhan V, Tabatabai ZL, Souers RJ, Thomas N, Wilbur DC, Moriarty AT. Trends in Cervical Cytology Screening and Reporting Practices; Results From the College of American Pathologists 2011 PAP Education Supplemental Questionnaire. *Arch Pathol Lab Med.* 2016;140:13–21.
22. Cervical screening programme, Department of health, The government of the Hong Kong in special administrative

region

23. Renshaw AA. Comparing Methods to Measure Error in Gynecologic Cytology and Surgical Pathology. *Arch Pathol Lab Med.* 2006; 130:626–629.
24. Cervical Cytology EQA scheme; Principles and Protocols. NHS, Scotland 2015.
25. Von Karsa L, Arbyn M, DeVuyst H, Dillner J, Dillner L, Franceschi S, Patnick J, Ronco G, Segnan N, Suonio E, Törnberg S, Anttila A. European guidelines for quality assurance in cervical cancer screening. Summary of the supplements on HPV screening and vaccination. *Papillomavirus Research* 2015; 22–31
26. Clary KM, Silverman JF, Liu Y, Sturgis CD, Grzybicki DM, Mahood LK, Raab SS. Cytohistologic Discrepancies; A Means to Improve Pathology Practice and Patient Outcomes. *Am J Clin Pathol* 2002;117:567-573.
27. Tan KB, Chang SAE, Soh VCH, Thamboo TP, Nilsson B, Chan NHL. Quality Indices in a Cervicovaginal Cytology Service; Before and After Laboratory Accreditation. *Arch Pathol Lab Med.* 2004;128:303–307.
28. Assuring quality of examination procedures. In: National accreditation Board for testing and calibration laboratories. (NABL 112). Specific criteria for accreditation of medical laboratories. 2012; 28.
29. Conduct of quality assurance visits. In: Guidelines for quality assurance visits in the cervical screening programme. NHS Cancer Screening Programmes, Sheffield. NHSCSP publication No 30 October 2008; p9-11.
30. <https://slidehunter.com/topics/deming-cycle> (13/07/2017)