Quality Assurance And Control In The Cytology Laboratory

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A Brief History

- CLIA 67: mandates 10% rescreening
- Wall Street Journal article in 1987 exposes shoddy and unethical laboratory practices
- CLIA 88: Clinical Laboratories Improvement Amendments of 1988, Final Rule 1992
CLINICAL LABORATORY IMPROVEMENTS AMENDMENTS OF 1988 (CLIA 88)

- CLIA ‘88 considers cytology high complexity testing. Cytology covered by all mandates applying to high complexity testing
- Other mandates governing cytology laboratories:
  - Location of cytology testing, methods of slide preparation and staining, retention of records
  - Personnel requirements and duties
  - Established workload limits based on performance evaluations
  - Hierarchical review of gynecological cases reactive or higher and all non-gynecological cases
  - Quality control and quality assurance practices
  - Statistical reports
  - Proficiency testing
MANDATED QUALITY CONTROL PRACTICES
CLIA 88 Section 493.1257

• Designed to reduce laboratory component of errors contributing to false negatives

• Core composed of three exercises in slide re-examination
  – Minimum of 10% of negative cases to be rescreened including random and high-risk
    • high risk generally defined as H/O abnormal cervical cytology or other risk factors for developing cervical cancer
  – 5-year retrospective review of cases diagnosed as HSIL or higher
  – Cytology-histology correlation
QUALITY CONTROL

- Quality control is a system for verifying and maintaining a desired level of quality in a test or process. Quality control practices span the entire testing process, from collection to the time the clinician receives the report.
QUALITY ASSURANCE

• Quality assurance is defined by CAP as systematic monitoring of QC results and quality practice parameters to assure that all systems are functioning appropriately. QA is the coordinated effort to bring together the various activities in the lab that are designed to detect, control and prevent the occurrence of errors.
Assessment of QC Practices

• Centers for Disease Control and Prevention awarded The College of American Pathologists (CAP) a cooperative agreement
• Goal: develop an inventory of current practices in gynecologic cytology laboratories to attempt to standardize procedures for quality improvement.
  – identify what quality metrics are collected
  – how metrics are analyzed
  – what benchmarks are used to determine variance in performance
  – and what actions are taken to address performance issues.
• Multistep process to determine consensus practices in QA for gynecologic cytology.
10% RESCREEN
CLIA 88 – Sec 493.1274 (c)1

- Mandates at least 10% of cases screened by a cytotechnologist be rescreened by a qualified supervisory cytotechnologist or pathologist prior to sign-out
  - Depends on state regulations, more rigorous regulations supercede CLIA

- Composed of random and high-risk
  - Definition of high risk varies, usually H/O of SIL

- Must be prospective and results included in final report

- Not done by the same person who screened slide

- Goal is to identify cytotechnologists with a high error rate
Rescreen: Results of Reviews
CLIA 88 – Sec 493.1274 (c)4,5,6 and (d)

• Records of all rescreening results must be documented
• There must be an annual statistical evaluation of the number of reviews of any NILM cases reclassified as LSIL+
• These reviews are compared as individuals against the laboratories’ overall statistics, and are one of the elements used to determine workload limits
CAP Checklist
CYP.07478

• Essentially the same as CLIA regulations
• Difference: Slides screened by MD certified in AP and qualified as a technical director do not need to be rescreened
10% Rescreen: Drawbacks

- Criteria for high-risk patients are not defined and standardized
- % of rescreen that should be high-risk is also not defined or standardized
- Not effective
  - Identification of poor screening performance may not occur quickly enough to be of benefit
    - Ten years to identify cytotechnologist with a high error rate [Melamed 1981]
  - False negative rate of the rescreen process far exceeds the false negative rate of primary screening (21% in one study)
  - Potential for >90% of errors to remain undetected
  - Inherent bias
10% Rescreen: Alternatives

- Better if threshold set at ASCUS and adequacy and infections included [Krieger 1994, Krieger 1998]
- Alternatives include:
  - 100% rescreen
  - Computer-assisted rescreening
  - Sharing cases among laboratories
RETROSPECTIVE REVIEWS
CLIA 88 – Sec 493.1274 (c)3

• CLIA mandates documented retrospective review of all negative gynecological specimens received in the preceding 5-years for patients with documented HSIL or above

• If significant discrepancies are found, which affect current patient care, an amended report must be issued
  – E.g.: currently HSIL but last year patient had adenocarcinoma or currently HSIL but last year patient had invasive cancer
Retrospective Review

- Generally less controversial than prospective review
- Cytologist errors detected at a higher rate than with prospective rescreening
- Sources of error include screening and interpretative
  - High rates of poorly prepared smears with compromising factors including obscuring inflammation and blood
  - A significant number of unsatisfactory Pap tests interpreted as NILM
  - Presence of few abnormal cells and “under-interpretation” of atypical immature squamous metaplasia
Retrospective Review

- False negative rates: 10 to 94%
  - Depends on trigger used
    - 53% false negatives (ASCUS threshold); 25% rate of unsat Paps called NILM [Sherman and Kelly] 1992
    - 38% false negatives (ASCUS/AGUS threshold) [Tabbara and Sidaway 1996]
    - 94% false negatives detected in 17 cases examined [Hatem and Wilbur 1995]
    - CAP Q-probe 20.4% false negatives [Jones 1995]
RETROSPECTIVE REVIEWS
Drawbacks and Alternatives

• Intensity of rescreening affects likelihood of detecting an abnormality
• 5-years may not be necessary
  – 2-year identified 75% [Allen 1994]
  – 3-year identified 94% [Tabbara and Sidaway 1996] or 86% [Jones 1995]
Prospective and Retrospective Review of Gynecologic Cytopathology

Findings From the College of American Pathologists Gynecologic Cytopathology Quality Consensus Conference Working Group 2

Jennifer A. Brainard, MD; George G. Birdsong, MD; Tarik M. Elsheikh, MD; David A. Hartley, CT(ASCP); Kalyani Naik, MS, SCT(ASCP); Margaret H. Neal, MD; Rhona J. Souers, MS; Michael R. Henry, MD

• Context.—Two quality metrics for gynecologic cytology are the subject of this review: “prospective rescreening” and “retrospective rescreening.”

Objective.—To offer consensus best practice approaches based on the College of American Pathologists’ laboratory-based survey funded by the Centers for Disease Control and Prevention.

Design.—The College of American Pathologists submitted a paper-based survey to 1245 laboratories. After review of initial results, follow-up Web-based survey results, and a literature review, consensus best practice statements were presented at a national consensus conference. These statements were discussed and voted upon by conference participants.

Results.—A total of 541 laboratories responded to survey questions about prospective and retrospective rescreening. Most laboratories (>85%) prospectively rescreen more than 10% of Pap tests interpreted as negative for intraepithelial lesion or malignancy. Most (72%) report inclusion of less than 20% high-risk cases. Most laboratories use multiple measures to define “high risk.” Most laboratories (96.2%) retrospectively rescreen Pap tests from the preceding 5 years only. In most laboratories (71.4%) only Pap test results with high-grade squamous intraepithelial lesion or worse prompt retrospective review.

Conclusions.—The number of Pap tests from high-risk patients should be maximized in prospective and retrospective rescreening. Unsatisfactory Pap tests should also be included. All readily identifiable high-risk human papillomavirus–positive cases with an interpretation of negative for intraepithelial lesion or malignancy should be prospectively rescreened. Cervical biopsy results with high-grade cervical intraepithelial neoplasia or worse (CIN 2+) should trigger retrospective rescreening. Regular feedback should be provided to cytotechnologists and cytopathologists. Upgraded diagnoses from negative for intraepithelial lesion or malignancy to atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion, should be monitored.

Recommendations to Enhance Prospective Rescreening

- Maximizing the number of high risk cases rescreened increases the power of this QA metric
- The laboratory should include all high risk cases in its rescreen pool
Recommendations to Enhance Prospective Rescreening

- Use multiple measures to identify patients at high risk
- Suggested high risk criteria:
  - Clinical risk factors
  - Prior HSIL cytology
  - Prior CIN 2+ biopsy result
  - Recent/concurrent hrHPV positivity
  - No screening in past 5 years
  - Unsatisfactory Paps
Recommendations to Enhance Prospective Rescreening

• Remove patients who no longer meet high risk criteria
  – No uniform criteria
  – Removal after consecutive negative PAP smears
  – Consecutive negative PAP smears and negative hrHPV results
  – 3 years from the last identified criterion for high-risk status
Recommendations for Tracking Results

• No consensus on monitoring upgrades to ASCUS
• Consensus reached: Results of prospective review should be shared with individuals, including cytotechnologists and cytopathologists at regular intervals
Retrospective Review: Enhancement

• Add cervical biopsy results of CIN 2+ to trigger retrospective review, in addition to cytology triggers
• Include unsatisfactory PAPs in the retrospective review
Recommendations for Tracking Results of Retrospective Review

• Tracking of upgrades from NILM to LSIL+ required by CLIA
  – Add tracking of upgrades from NILM to ASCUS-H
• This metric should be monitored for both both cytotechnologists and pathologists
  – Monitoring of upgrade rates for pathologists very low
  – Most studies report interpretive errors in which pathologists play a role
• Results of these reviews should be shared regularly
• Constant monitoring of trends in false negative rates is required
• Lab must compare all pre-malignant and malignant gynecological cytology reports with subsequent histology
• Definitions of SIL and a discrepancy are documented in the lab manual
• May be prospective or retrospective
• If in-house specimens are not available, the lab is required to obtain follow-up from the referring clinician on patients with a diagnosis of HSIL or cancer
CAP Checklist

• CYP. 07543
  – Records of attempts to obtain and review follow-up histological reports or materials are available within the laboratory when gynecological cases with high-grade squamous intraepithelial lesion (HSIL) or malignant cytological findings are reported.

• CYP .07556 Additional Reports/Material Unavailable
  – When a follow-up histological report or material is not available within the laboratory, there are records of attempts to obtain follow-up histological information for correlative review when gynecologic cases with significantly abnormal (HSIL) or malignant cytological findings are reported.
Quality Improvement Opportunities in Gynecologic Cytologic-Histologic Correlations
Findings From the College of American Pathologists Gynecologic Cytopathology Quality Consensus Conference Working Group 4

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• Context.—Cytopathology experts, interested stakeholders, and representatives from the College of American Pathologists, the Centers for Disease Control and Prevention, the American Society of Cytopathology, the Papanicolaou Society of Cytopathology, the American Society for Clinical Pathology, and the American Society of Cytotechnology convened the Gynecologic Cytopathology Quality Consensus Conference to present preliminary consensus statements developed by working groups, including the Cytologic-Histologic Correlations Working Group 4, using results from surveys and literature review. Conference participants voted on statements, suggested changes where consensus was not achieved, and voted on proposed changes.

Objectives.—To document existing practices in gynecologic cytologic-histologic correlation, to develop consensus statements on appropriate practices, to explore standardization, and to suggest improvement in these practices.

Data Sources.—The material is based on survey results from 546 US laboratories, review of the literature from 1988 to 2011, and the College of American Pathologists Web site for consensus comments and additional survey questions.

Conclusions.—Cytologic-histologic correlations can be performed retrospectively, during initial case review, or both. At minimum, all available slides should be reviewed for a high-grade squamous intraepithelial lesion Papanicolaou test with negative biopsies. The preferred monitor for correlations is the positive predictive value of a Papanicolaou test. Laboratories should design cytologic-histologic correlation programs to explore existing or perceived quality deficiencies. (Arch Pathol Lab Med. 2013;137:199-213; doi: 10.5858/ arpa.2012-0250-OA)
Consensus Statements

- May be real time, retrospective, or both
- At a minimum, review all available slides for high-grade squamous intraepithelial lesion (HSIL) Pap tests with negative biopsies, with a correlation interval between three to four months but not exceeding six months.
- Standardization of CHC and its metrics is desirable.
- The positive predictive value of a positive Pap test is the preferred standard CHC metric, and laboratories should use the PPV for the whole laboratory to formulate QA monitors.
Consensus Statements

• It is desirable to provide timely notification to a caregiver for confirmation of a negative biopsy and HSIL or cancer (HSIL+) Pap test, or of a negative biopsy and an HSIL or cancer Pap test re-interpreted as NILM (negative for intraepithelial lesion or malignancy).

• Laboratories should attempt to obtain correlation biopsy information for all patients with an HSIL or cancer Pap test.
Consensus Statements

• Microscopic review of all slides from discordant Pap test/cervical biopsy pairs (as laboratory-defined) is desirable for CHC.

• CHC is optimal with a multilayered approach.
Curiosity may prompt further CHC investigations.

- For example, how often does your laboratory have an LSIL Pap test but an HSIL biopsy?
- Was the Pap test interpreted as LSIL because of few HSIL cells on the slide, or are HSIL cells usually absent?
- How many ASC-H Pap tests have an HSIL biopsy, and what does review of those Pap tests reveal?
- Other pairs that might be interesting to monitor to improve laboratory performance are AIS/LSIL, atypical squamous cells of undetermined significance (ASC-US) with a positive test for human papillomavirus (HPV+) and a SIL biopsy, ASC-US with a negative test for HPV and a SIL biopsy, atypical glandular cells (AGC) and subsequent endocervical or endometrial biopsies, and HSIL
- Pap tests in pregnant or postpartum women. Any of these monitors can be periodic or continuous, depending on other laboratory metrics or conditions.
PROFICIENCY TESTING

• Mandated by CLIA for individuals examining gynecologic cytology
• No national system exists
• State and private programs
  – State of Maryland Gynecologic Proficiency Program (HCFA)
  – State of New York
  – CAP
  – CytoQuest from continuing Education in Cytology
  – CheckSample, CheckPath and STAR from ASCP
Proficiency Testing

- Implementation delayed nearly 20 years
  - Test needed to adequately address the subjective nature of cytologic interpretation and replicate normal working conditions
- Not implemented until 2005
- 2006 College of American Pathologists (CAP) PAP PT program for cytopathology shows that 99.6% of test takers pass in 3 attempts or less
- The rate of an initial unsuccessful test has declined over time to 2% to 7%. 
The Role of Proficiency Testing in Ensuring Quality

Findings From the College of American Pathologists Gynecologic Cytopathology Quality Consensus Conference Working Group 3

Lydia Pleotis Howell, MD; Ritu Nayar, MD; Lynnette Savaloja, CT(ASCP); Sana Tabbara, MD; Nicole Thomas, MPH, CT(ASCP); Barbara Winkler, MD; Joseph Tworek, MD

Context.—Implementation of proficiency testing for gynecologic cytology was delayed 20 years because of challenges addressing the subjective nature of cytologic interpretation and replicating normal working conditions. Concern remains regarding test scoring, slide validation, test environment, and other issues. How these test results are, or should be, used in quality management has never been explored.

Objective.—To provide information on good laboratory practices for gynecologic cytology proficiency testing based on findings from the College of American Pathologists’ survey-based project funded by the Centers for Disease Control and Prevention.

Data Sources.—An expert working group evaluated results from a Web-based, national laboratory survey plus responses from follow-up questions and findings from the literature. The group created statements on good laboratory practices pertinent to proficiency testing and its role in quality management, which were discussed and voted on at a consensus conference.

Conclusions.—Two-thirds of laboratories report having an individual with an unsuccessful proficiency testing score. More than 90% did not initiate any remedial action for 1 or 2 unsuccessful tests; 84% of laboratories reported they actively monitored results from proficiency testing, but most laboratories did not initiate any remedial action for cytotechnologists (81.4%; 376 of 462) or pathologists (87.7%; 405 of 462) who passed a proficiency test but who did not score 100%. Proficiency testing pass-fail rates should be monitored globally for the laboratory and for each individual. Proficiency testing slides should be prescreened by cytotechnologists for pathologists who are not primary screeners. Remedial action should not be required for a passed, but imperfect, test. No remedial action is required for an unsuccessful, first proficiency test result before retesting.

Consensus Recommendations

The laboratory should have a written policy that the director (and/or designee) actively monitors results of gynecologic cytology proficiency testing.

2. Pap PT pass-fail rates should be monitored globally for the laboratory and by individual practitioner (ie, CT and pathologist).

3. Pap PT slides should be prescreened by CTs for pathologists who are not primary screeners.

4. For an unsuccessful first-time taker of PT (CTs and pathologist):
   a. Enrollment and retesting, as required by CLIA, is sufficient.
   b. No other remedial actions are required, unless supported by other quality indicators.
Consensus recommendations cont.

5. Remedial action should not be required for a passed-but-imperfect test result (ie, score of <100%), even for multiple, nonperfect test scores.

6. Monitoring of incorrect slide diagnoses on passed PT tests:
   a. Is discouraged from inclusion in laboratory PT policy.
   b. No intervention for this test finding is necessary.

7. For laboratories performing more than one slide methodology, each methodology should be tested during PT.

8. There is room for improvement in using PT testing methods as a monitor, especially in light of new screening technologies.
Critiques of PT

- No evidence that human performance deteriorates after one year
- Does not acknowledge uncertainty inherent in screening
- Routine cytology practice is collaborative
- Appeals show lack of reliability and reproducibility in some slides
- Scoring system
  - Difficulty in distinguishing LSIL from HSIL
  - 6% failure rate for certain slides
- Gaming the system
  - Overcalling rather than undercalling, 5 points instead of 10 points
- Onerous and meaningless quality indicator.
- PT is effective in identifying individuals who cannot identify abnormal cells and that most individuals who perform cytology testing do high quality work.
Summary

• Prospective and retrospective reviews and CHC are an important part of QC in the cytology lab
• Recommendations for enhancing prospective and retrospective reviews may improve the educational value of these processes.
• CHC useful quality metric
  – Measure PPV
  – Can expand the correlations beyond HSIL and above
• PT onerous and meaningless, but we still have to do it.