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Five-year retrospective review in gynecologic cytopathology: is it time to amend?

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Introduction According to the Clinical Laboratory Improvement Amendments 1988 regulations, 5-year retrospective review (5YRR) of normal Papanicolaou tests in patients with a newly diagnosed high grade squamous intraepithelial lesion or above (HSIL+) is mandatory. Since this mandate has been in place, a multitude of changes have taken place in the screening and management guidelines of cervical cancer. The aim of this study is to assess the role of this mandate in our laboratory and to investigate the lessons learned.

Material and methods The cytopathology electronic database and institutional quality assurance records at Loyola University Medical Center were searched from January 2009 to December 2019 to identify all Papanicolaou tests diagnosed as new "HSIL and above" (HSIL+). Major discrepancy (2+) was defined as initial negative diagnosis changed to HSIL+.

Results A total of 153,083 Papanicolaou tests were performed during this period; out of these, 1452 (0.94%) were diagnosed as HSIL+. A total of 695 HSIL+ Papanicolaou tests had a negative prior Papanicolaou and in 615 of 695 there was agreement with the initial negative diagnosis. In 61 Papanicolaou tests, the initial diagnosis was changed from negative and they were reclassified on review as 3 HSIL, 9 ASC-H, 7 AGC, and 42 ASCUS or LSIL. Major discrepancy rate was calculated as 3 of 695 (0.43%). None required an amended report.

Conclusions It is important to revisit the 5YRR as a method of implementing the quality indicators in gynecologic cytology so that the process retains its value without overburdening cytology laboratories and personnel.

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Introduction

Legislations governing laboratories have been around for more than 60 years and included the Health Insurance for the Aged (Medicare Act of 1965) and the Clinical Laboratory Improvement Act of 1967.[1] Although the scope of their oversight was limited, the federal and state government laboratories or physician laboratories were for the most part excluded from their purview.

It was only after a series of articles about "Pap mills" published in the *Wall Street Journal* in 1987 exposing the substandard practices in gynecologic cytology that the government took note.[2] The Clinical Laboratory Improvement Amendments of 1988 (CLIA 88) introduced national standard for cytology laboratories and laid emphasis on proficiency testing. The final regulations of CLIA 88 were published in 1992 and, except for minor modifications in 2003, have essentially remained unchanged for the past 30 years. The Centers for Medicare and Medicaid (CMS) is responsible for the implementation of these standards.

As mandated by the CLIA 88, gynecologic cytology laboratories are required to report a number of quality metrics. According to these regulations, 5-year retrospective review of normal Papanicolaou tests in patients with a newly diagnosed high-grade squamous intraepithelial lesion (HSIL) or cancer is mandatory.[3]

All previous negative Papanicolaou tests (either onsite or in storage) from the past 5 years must be screened for each current premalignant or malignant diagnosis. If a significant discrepancy is found that will impact current patient care, the clinician must be notified, and an amended report issued. In most cases, results of this retrospective review do not change current patient management, and amended reports are not necessary; nevertheless, records of all rescreening results must be documented.[3]

The College of American Pathologists (CAP), as part of the Laboratory Accreditation Program, essentially reiterates these CLIA regulations as specific checklist requirements, namely, CAP checklist items *CYP.07517 Retrospective review* and *CYP.07530 Retrospective review requiring amendment.*[4]

The discrepancies are called significant if a high-grade lesion or cancer is discovered on prior samples on rescreening. Low-grade lesions and atypical diagnosis are not felt to represent a significant discrepancy. It is left up to the individual laboratory to determine what would constitute a significant discrepancy. This mandatory requirement affects all aspects of a cytopathology laboratory including time and labor spent retrieving the slides, re-reviewing and reporting the results. This can affect the turnaround time of the new cases including non-gynecologic cytology as well as affect the workload of the cytotechnologists.

Although this 5-year retrospective review (5YRR) serves as a quality monitor as well as an educational tool for laboratories, in the current scenario of shrinking pathology workforce and increasing workload in non-gynecologic cytology specimens, the value of this retrospective review needs to be reassessed. Additionally, since this mandate has been in place, a multitude of changes have taken place in the screening and management guidelines of cervical cancer, including the latest 2019 ASCCP guidelines, availability of human papillomavirus (HPV) vaccination, and the utilization of HPV cotesting and primary HPV testing.[5] These major changes have led to lengthened screening periods, making this mandate somewhat outdated. The aim of this study is to assess the role of this mandate in our laboratory and to investigate the lessons learned.

Material and methods

The cytopathology electronic database and institutional quality assurance records at Loyola University Medical Center were searched from January 2009 to December 2019 to identify all Papanicolaou tests diagnosed as new HSIL or higher (HSIL+), which included HSIL, squamous cell carcinoma, adenocarcinoma, and other malignancies. A new HSIL+ was defined as a Papanicolaou test without a previous history of abnormal Papanicolaou results including atypical squamous cells of undetermined significance (ASCUS), atypical squamous cells, high grade cannot be excluded (ASC-H), atypical glandular cells (AGC), or low-grade squamous intraepithelial lesion (LSIL). All the corresponding prior negative Papanicolaou tests from the same patient within the last 5 years were included in the 5YRR. Fig. 1 shows the study design.

All the Papanicolaou tests until March 2019 were prepared on the ThinPrep Processor 3000 (Hologic, Marlborough, MA) and after that on ThinPrep Processor 5000 (Hologic). The specimens for Papanicolaou testing were collected by the clinicians in a vial filled with PreservCyt solution (Hologic). The slides were then interpreted by a cytotechnologist (CT) and, if needed, by a board-certified cytopathologist.

The slides, where available, were reviewed to identify discrepancies between the initial diagnosis and the subsequent review. The discrepancies were defined as minor (1+) when the initial diagnosis was negative and on review was changed to ASCUS/LSIL/ASC-H/AGC. Major discrepancy (2+) was defined as initial negative diagnosis changed to HSIL+. For the purpose of the current study we limited the discrepancies to the "major discrepancies" (2+). Board certified cytopathologists with >10 years of experience and the technical supervisor of the cytology laboratory re-reviewed all available slides. For all cervicovaginal cytology specimens The Bethesda System for reporting Cervical Cytology was used for diagnoses and classification.[6]

Results

During the collection period (2009-2019), 153,083 Papanicolaou tests were reviewed in our laboratory. The total

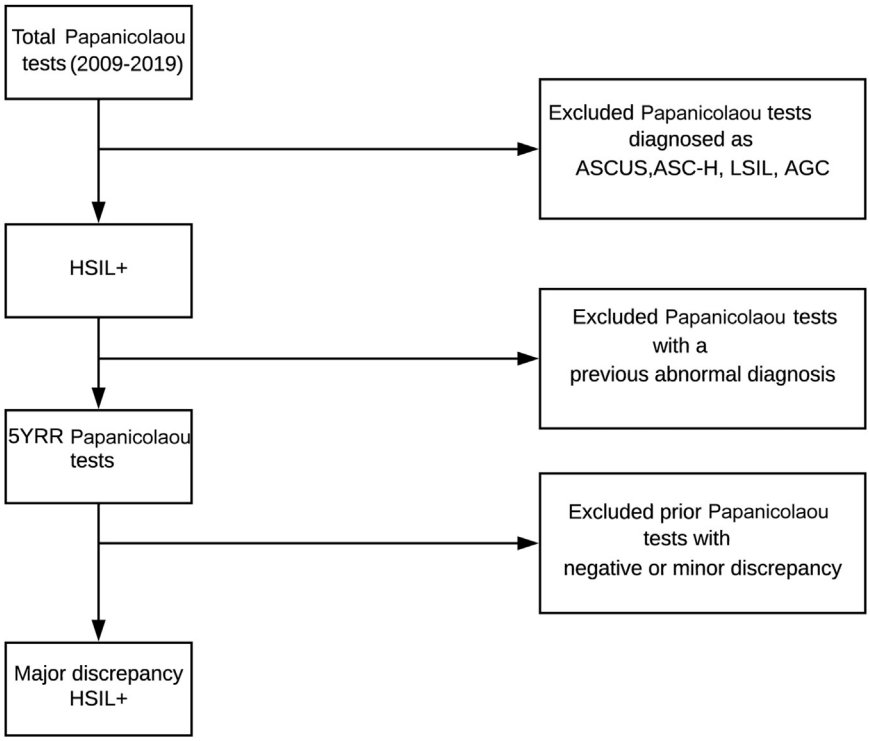

Figure 1 Flow chart showing the study design and exclusion criteria.

number of HSIL+ diagnosed were 1452 (0.94%). Fig. 2 shows the breakdown of these tests. There were 133,444 negative Papanicolaou tests. The atypical category included ASCUS, ASC-H, and AGC, for a total of 10,582 tests. The positive category (6240 of 153,083; 4.08%) included LSIL (4673 of 6240; 82.43%), HSIL (1452 of 6240; 23.27%), adenocarcinoma (57 of 6240; 0.91%), squamous cell carcinoma (39 of 6240; 0.63%) and others (19 of 6240; 0.30%). The "others" category comprised Papanicolaou tests diagnosed as poorly differentiated carcinoma or positive for malignancy without further classification. We excluded 757 out of 1542 (52.13%) HSIL Papanicolaou tests from review as they had a previous known abnormal diagnosis. A total of 695 of 1452 (47.87%) Papanicolaou tests of HSIL+ with a prior negative Papanicolaou test were included in the study. Fig. 3 shows the breakdown of these

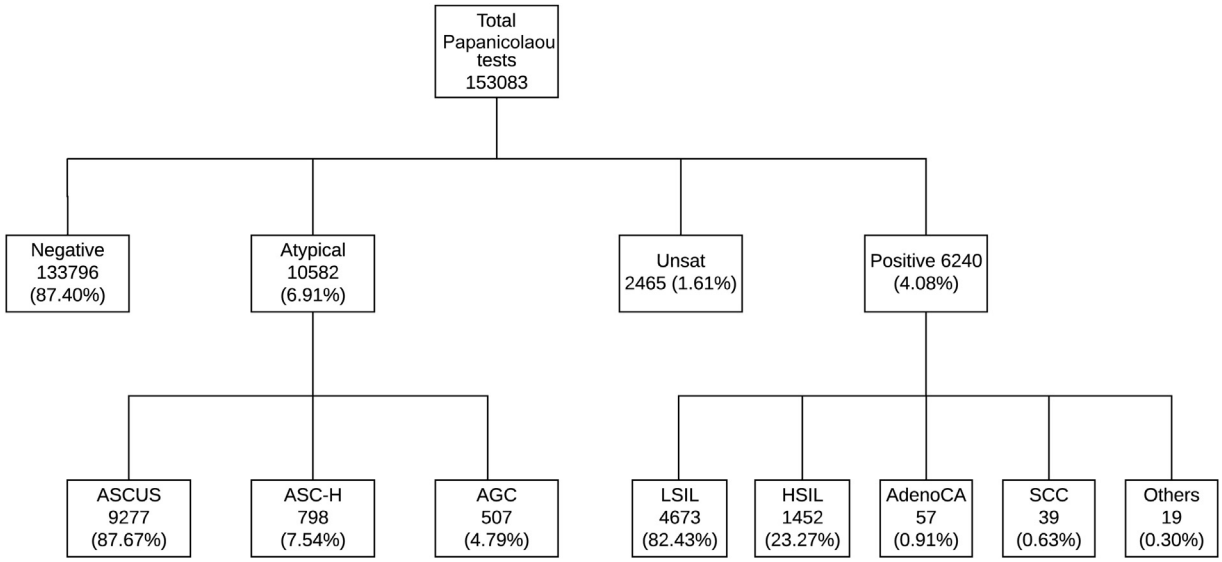

Figure 2 The total number of Papanicolaou tests that were reviewed at Loyola University Medical Center during 2009-2019 and their results.

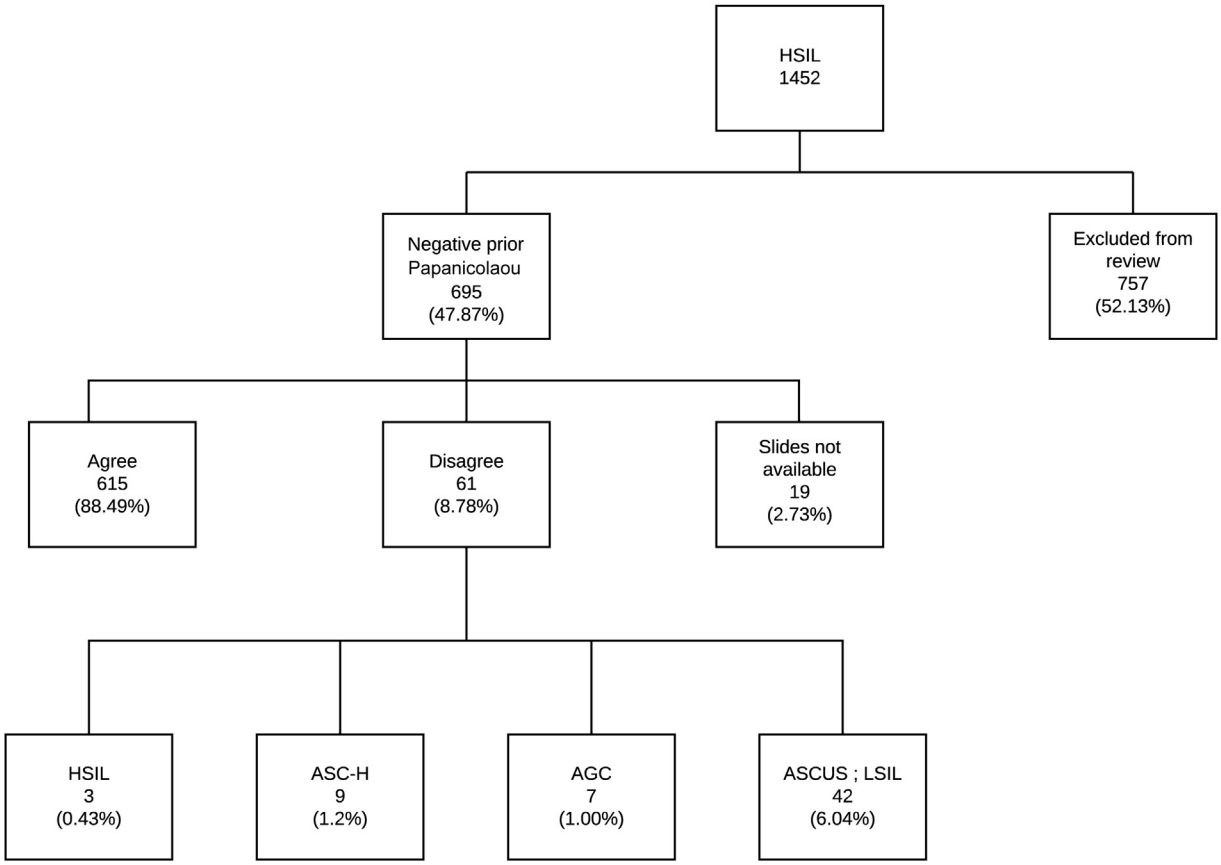

Figure 3 Total number of HSIL+ Papanicolaou tests diagnosed during 2009-2019 and results of the 5YRR.

Papanicolaou tests. There was agreement in 615 of 695 (88.49%) Papanicolaou tests with the initial negative diagnosis. In 61 of 695 (8.78%) Papanicolaou tests the initial diagnosis was changed from negative to an abnormal diagnosis. We were unable to locate the slides for the remaining 19 Papanicolaou tests.

Out of 61 Papanicolaou tests that were reclassified, 3 were HSIL, 9 were ASC-H, 7 were AGC. ASC-H Papanicolaou tests showed between 1 and 9 morphologically abnormal cells that were small with variable nuclear to cytoplasmic ratios and irregular nuclear contours. The chromatin was coarse and hyperchromatic. Because of paucity of the abnormal cells these were classified as ASC-H. This could represent sampling error. The surgical pathology follow up was available for 5 out of 9 patients (1 endometrial adenocarcinoma, 3 HSIL, and 1 focal atypia, no HSIL). Out of 7 Papanicolaou tests that were reported as AGC on review, 3 showed small tight clusters of abnormal cells with significant overlapping, nuclear enlargement and vacuolated cytoplasm, consistent with atypical endometrial cells. The remaining 4 were classified as AGC not otherwise specified with no further classification as the cells were poorly preserved with degenerative changes. No dysplastic squamous cells were noted in the background. The new HSIL+ Papanicolaou test diagnosis that they preceded were adenocarcinoma, favor endometrial (3), AGC not otherwise specified (2), and AGC favor endometrial cells (1). Five of these Papanicolaou tests had a surgical pathology follow-up consistent with endometrial adenocarcinoma, and one showed a malignant mixed Müllerian tumor. The remaining 42 of 695 (6.04%) were either LSIL or ASCUS. The HPV status was available for 6 of 61 discrepant cases and 5 were positive for high-risk HPVs (HrHPV) while in 1 case HPV was not detected. Major discrepancy rate was calculated as 3 of 695 (0.43%). All the negative Papanicolaou tests that were reclassified as HSIL+ on review were within 2.5 years of the current HSIL diagnosis. None of the Papanicolaou tests that were reclassified required an amended report. The average ASCUS to SIL ratio at our institute during this time period was 1.5 (range, 1.04-2.06)

Discussion

CMS is the main accrediting agency for all laboratories in the United States.[7] The laboratories must be compliant with the CLIA statute and this compliance is inspected by professional agencies like CAP and Joint Commission.[3,4,8] The initial CLIA regulations were passed in 1967 and have undergone several amendments since then. The CLIA amendments of 1988 were the direct result of a number of

articles in the news about the suboptimal practices and reporting in gynecologic cytology laboratories.[2]

The 5YRR serves as an educationally valuable tool for the laboratory as well as a quality metric.[9] It aims to improve the quality of the Papanicolaou tests by evaluating the laboratory and individual performances.[10] It aims to reduce the false-negative rates and to improve the primary screening process by identifying and correcting the mistakes. The findings of the CAP Gynecologic Cytopathology Quality Consensus conference from 2013 showed that 96.2% of the laboratories in the United States review Papanicolaou tests from the past 5 years.[11]

Several studies have attempted to evaluate the utility of retrospective screening as well as the false negative rates in prior Papanicolaou tests. In the CAP Q-probes study by Jones, the majority (86%) of the false negatives were identified from Papanicolaou tests obtained in the last 3 years before the HSIL diagnosis.[12] Tabarra et al[13] found that limiting the review to the last 3 years before a new HSIL diagnosis can detect 94% of the underdiagnosed cases. In a study by Allen et al,[10] 75% of the cases reclassified as HSIL were within the 2 years of diagnosis of HSIL. Hatem and Wilbur[14] looked at the negative Papanicolaou tests immediately preceding (within 2 years) the HSIL diagnosis. Five cases out of 17 (31%) were upgraded to moderate to severe dysplasia on review. Sherman and Kelly[15] looked at prior 3 negative Papanicolaou tests before a HSIL diagnosis and found that 22.7% of the Papanicolaou tests revealed a squamous intraepithelial lesion on review. Both studies had similar findings; the reasons for false negatives included very few abnormal cells, poor preparation, obscuring inflammation, and unsatisfactory Papanicolaou tests.[14,15] Another study by Montes et al[16] looked at the prior Papanicolaou findings from 100 cases subsequently diagnosed as HSIL. They found that immature metaplastic cells were the most overlooked abnormality, and these could represent HSIL cells. To summarize, false-negative rates on prior Papanicolaou tests from newly diagnosed HSIL have ranged from 20% to 94%, respectively. All these studies clearly demonstrate that most false-negative Papanicolaou test findings occur within 3 years of the current abnormal Papanicolaou test. Most of the false negatives are reclassified as ASCUS; and HSIL is a diagnosis in minority of the re-reviews.[17] There is strong evidence to suggest that looking beyond 3 years is unlikely to add value to this quality measure.[10-19]

Squamous cell carcinoma of the cervix has a well-documented natural progression history.[20,21] Available data suggest that more than 90% of individuals with genital HPV infections are asymptomatic and clear the infection within 2 years.[22,23] High-grade cervical intraepithelial neoplasia (CIN3) are caused mostly by high-risk HPVs (hrHPV), which include HPV16 and HPV18 among others. In 10% to 20% of women, these infections remain persistent and are at risk of progression to grade 2-3 cervical intraepithelial neoplasm (CIN) and eventually to invasive cancer of the cervix. A study by Castle et al[24] looked at detection of HPV16 and subsequent progression to a squamous intraepithelial lesion. They found that for HPV16, which is the most carcinogenic, the absolute risk is around 40% after 3-5 years of persistent infection. Khan et al[25] have shown, following a cohort of more than 20,000 women, that the 10-year cumulative incidence rate of CIN3 or cancer was 17% among women who tested positive for HPV16 at enrollment, while it was 14% and 3% among women who tested positive for HPV18 and other carcinogenic HPV types, respectively. Another study by Bulk et al[26] looked at the negative Papanicolaou tests preceding an HSIL diagnosis and found that hrHPV was present in 80% of negative Papanicolaou tests preceding CIN2/3 diagnosis. The long latency of the HPV infection and subsequent development of cancer makes it amenable to early detection by cytology and HPV testing.

The detection of HPV infection has greatly improved with the advent of widespread hrHPV testing.[27] It is recommended as a primary screening modality for detection of precancerous cervical lesions.[28,29] Multiple meta-analyses have demonstrated that HPV testing alone or with concurrent cytology is associated with increased detection of these lesions.[30,31] Currently, different societies have established guidelines for optimal screening strategies in the United States. The American Cancer Society Guidelines recommend that individuals with a cervix start cervical cancer screening at age 25 years and undergo primary HPV testing every 5 years through age 65 years. Cotesting (HPV testing in combination with cytology) every 5 years or cytology alone every 3 years is recommended for individuals aged 25-65 years in case primary HPV testing is not available.[32] The United States Preventive Services Task Force recommends screening every 3 years with cervical cytology alone in women aged 21-29 years. It recommends screening with cervical cytology alone every 3 years or hrHPV testing alone every 5 years for women aged 30-65 years.[33] The latest ASCCP 2019 guidelines recommend risk-based guidelines for management of an abnormal cervical screening test.[5] As per these new guideline recommendations for colposcopy, treatment or surveillance will be based on the patient's risk of CIN3+. Increase surveillance with combination of cytology and concurrent HPV has improved the detection of squamous intraepithelial lesions. A recent study by Ogilvie et al[34] showed that the use of primary HPV testing compared with cytology testing resulted in a significantly lower likelihood of detection of HSIL and higher lesions at 48 months. Sawaya et al[35] showed that age-adjusted incidence rates of HSIL or worse were similar for women screened at 9-12 months (25 of 10,000), 13-24 months (29 of 10,000), and 25-36 months (33 of 10,000) after normal Papanicolaou tests (within 3 years). Also, cervical smears interpreted as HSIL or worse are rare, and the incidence rate is unrelated to the time since last normal Papanicolaou test. In our institution, on 5YRR, out of 695 tests that were originally reported as negative only 3 were reclassified as HSIL during a period of 10 years.

The HPV vaccine was approved by the US Food and Drug Administration in 2006. Although initially the vaccine uptake was slow in the United States, due to increasing efforts to educate the population regarding the benefits of the vaccine, the numbers have picked up. The 2018 National Health Interview Survey reported 39.9% of adults (aged 18-26 years) as having received 1 or more doses of the HPV vaccine.[36] A 2018 National Immunization Survey-Teen of adolescents aged 13 to 17 years showed that 68.1% of female and 51.1% of male patients were up to date with HPV vaccine based on HPV vaccine recommendations.[37] Emerging evidence shows significant declines in cervical abnormalities from countries with higher HPV vaccine uptake.[38,39] Additionally, the efficiency of cytology-based screening is reported to be much less in vaccinated populations. Of note, increased reporting of minor abnormalities caused by HPV types with lower cancer risk has been reported as well.[40] In the light of these findings, future recommendations for cervical cancer screening will need to factor in the effects of HPV vaccination.[32]

The practice of cytology is tightly regulated by the workload limits imposed on CTs. There has been a relative increase in the number of non-gynecologic cytology specimens in the recent years due to the increasing use of minimally invasive real-time image-guided techniques like endoscopic ultrasonography and endobronchial ultrasonography. Also, changes in the screening intervals and use of automated technologies for gynecologic cytology has decreased the volume of gynecologic cytology specimens. The CT daily workload and skills have continued to evolve and diversify to adequately address the changing needs of the cytolopathology practice.[41] According to current CLIA regulations, CAP checklist, and an ASC document on the taskforce for workload limits, CTs on an average spend 6.85 minutes/slide.[3,4,42-44] At our institute, CTs screen 7.5 slides/hour for 8 hours in a day and thus spend around 7-8 minutes per slide. The mandatory 5YRR requires CTs to spend considerable time and labor retrieving, re-reviewing, and reporting these results. In the current climate where the productivity of the employee is closely watched and documented, this adds an additional burden to the CT workload.

Current federal rule regarding the 5YRR states[3]:

> D5625 §493.1274 Standard: Cytology (c) (3) For each patient with a current HSIL, adenocarcinoma, or other malignant neoplasm, laboratory review of all normal or negative gynecologic specimens received within the previous 5 years, if available in the laboratory (either on-site or in storage). If significant discrepancies are found that will affect current patient care, the laboratory must notify the patient's physician and issue an amended report.

The terminologies "significant discrepancy" and "will affect patient care" has been left up to the individual laboratories to determine. However, most laboratories have reached an informal consensus that a finding of HSIL or higher in the 5YRR constitutes a significant discrepancy and could necessitate an amended report. Every laboratory must have a written policy in place addressing these issues and how they will report these.[7] In a vast majority of cases the recognition of an abnormality in the prior specimen, prompted by a newly identified lesion, will not change the current clinical management. Thus, an amended report is rarely if ever needed. Looking at the 10-year data from our institution, an amended report was never needed. In an editorial addressing if amended reports are ever necessary, Dr. Diane Davey also recommended that if nothing is accomplished in terms of current patient care, amended reports do not serve any purpose other than creating litigation issues.[45]

Although quality assurance remains an important part of practicing cytology laboratories, in the current health care scenario, it is important to revisit the methods of implementing these indicators. Although these quality assurance activities remain a mandatory requirement as per CLIA regulations, there is no financial reimbursement by the CMS for these activities. The focus should be on retaining as much information as possible without making the process burdensome. Hence the need is to optimally utilize the CT's time and effort without depreciating the value of the quality assurance initiatives. The time, money, and resources that are needed to perform these reviews could be significantly decreased without sacrificing the benefits of the quality assurance practices. With the advent of newer testing modalities, clinical guidelines, and management strategies in cervical cancer screening, and the ever-changing cytopathology practice needs, we believe it is time now to revisit the 5YRR rule.

References

1. Davey DD, Austin RM, Birdsong G, Zaleski S. The impact of the Clinical Laboratory Improvement Amendments of 1988 on cytopathology practice: a 25th anniversary review. *J Am Soc Cytopathol*. 2014;3:188−198.
2. Bogdanich W. Lax laboratories: the Pap test misses much cervical cancer through labs' error—cut-rate "Pap mills" process slides using screeners with incentive to rush—misplaced sense of security. *Wall Street J*; 1987.
3. Clinical Laboratory Improvement Amendments of 1988: final rule. *Fed Regist*; 1992. http://www.phppo.cdc.gov/clia/regs/toc.aspx. Accessed March 3, 2020.
4. CAP Accreditation Program. All common checklist and cytopathology checklist. College of American Pathologists. Available at: http://www.cap.org/web/home/lab/accreditation. Accessed March 3, 2020.
5. Perkins RB, Guido RS, Castle PE, et al. 2019 ASCCP Risk-Based Management Consensus Guidelines for abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis*. 2020;24:102−131.
6. Nayar R, Wilbur DC, eds. *The Bethesda System for Reporting Cervical Cytology*. 3rd ed. New York: Springer International Publishing; 2015.
7. U.S Department of Health and Human Services. Centers for Medicare and Medicaid Services. Clinical Laboratory Improvement Amendments of 1988 (CLIA) Proficiency Testing Regulations Related to Analytes

and Acceptable Performance - Proposed Changes. *Fed R*. 2019;84:1536−1567.
8. The Joint Commission. Facts about laboratory accreditation. Available at: https://www.jointcommission.org/accreditation/accreditation_main.aspx. Accessed March 30, 2020.
9. Davey DD. Papanicolaou smear 5-year retrospective review: what is required by the Clinical Laboratory Improvement Amendments of 1988? *Arch Pathol Lab Med*. 1997;121:296−298.
10. Allen KA, Zaleski S, Cohen MB. Review of negative papanicolaou tests. Is the retrospective 5-year review necessary? *Am J Clin Pathol*. 1994;101:19−21.
11. Brainard JA, Birdsong GG, Elsheikh TM, et al. Prospective and retrospective review of gynecologic cytopathology: findings from the College of American Pathologists Gynecologic Cytopathology Quality Consensus Conference Working Group 2. *Arch Pathol Lab Med*. 2013;137:175−182.
12. Jones BA. Rescreening in gynecologic cytology: rescreening of 3762 previous cases for current high-grade squamous intraepithelial lesions and carcinoma—a College of American Pathologists Q-probes study of 312 institutions. *Arch Pathol Lab Med*. 1995;119:1097−1103.
13. Tabbara SO, Sidawy MK. Evaluation of the 5-year review of negative cervical smears in patients with high grade squamous intraepithelial lesions. *Diagn Cytopathol*. 1996;15:7−10 [discussion: 10-1].
14. Hatem F, Wilbur DC. High grade squamous cervical lesions following negative papanicolaou smears: false-negative cervical cytology or rapid progression. *Diagn Cytopathol*. 1995;12:135−141.
15. Sherman ME, Kelly D. High-grade squamous intraepithelial lesions and invasive carcinoma following the report of three negative Papanicolaou smears: screening failures or rapid progression? *Mod Pathol*. 1992;5:337−342.
16. Montes MA, Cibas ES, DiNisco SA, Lee KR. Cytologic characteristics of abnormal cells in prior "normal" cervical/vaginal Papanicolaou smears from women with a high grade squamous intraepithelial lesion. *Cancer*. 1999;87:56−59.
17. Howell S, Theodor M, Pacey NF, Patwardhan JR, Ayer B. Quality assurance in cytology: rescreening of previously negative smears from high grade squamous intraepithelial lesions. *Acta Cytol*. 1997;41:1085−1090.
18. Wilbur DC. False negatives in focused rescreening of Papanicolaou smears: how frequently are "abnormal" cells detected in retrospective review of smears preceding cancer or high-grade intraepithelial neoplasia? *Arch Pathol Lab Med*. 1997;121:273−276.
19. Jones BA. Rescreening in gynecologic cytology. Rescreening of 8096 previous cases for current low-grade and indeterminate-grade squamous intraepithelial lesion diagnoses—a College of American Pathologists Q-Probes study of 323 laboratories. *Arch Pathol Lab Med*. 1996;120:519−522.
20. Moscicki AB, Schiffman M, Burchell A, et al. Updating the natural history of human papillomavirus and anogenital cancers. *Vaccine*. 2012;30(suppl 5):F24−F33.
21. Castellsagué X. Natural history and epidemiology of HPV infection and cervical cancer. *Gynecol Oncol*. 2008;110(3 suppl 2):S4−S7.
22. Rodríguez AC, Schiffman M, Herrero R, et al. Longitudinal study of human papillomavirus persistence and cervical intraepithelial neoplasia grade 2/3: critical role of duration of infection. *J Natl Cancer Inst*. 2010;102:315−324.
23. Schiffman M, Glass AG, Wentzensen N, et al. A long-term prospective study of type-specific human papillomavirus infection and risk of cervical neoplasia among 20,000 women in the Portland Kaiser cohort study. *Cancer Epidemiol Biomarkers Prev*. 2011;20:1398−1409.
24. Castle PE, Solomon D, Schiffman M, Wheeler CM. Human papillomavirus type 16 infections and 2-year absolute risk of cervical precancer in women with equivocal or mild cytologic abnormalities. *J Natl Cancer Inst*. 2005;97:1066−1071.
25. Khan MJ, Castle PE, Lorincz AT, et al. The elevated 10-year risk of cervical precancer and cancer in women with human papillomavirus (HPV) type 16 or 18 and the possible utility of type-specific HPV testing in clinical practice. *J Natl Cancer Inst*. 2005;97:1072−1079.
26. Bulk S, Rozendaal L, Zielinski GD, et al. High-risk human papillomavirus is present in cytologically false-negative smears: an analysis of "normal" smears preceding CIN2/3. *J Clin Pathol*. 2008;61:385−389.
27. Cuzick J, Myers O, Hunt WC, et al. Human papillomavirus testing 2007-2012: co-testing and triage utilization and impact on subsequent clinical management. *Int J Cancer*. 2015;136:2854−2863.
28. Castle PE, Stoler MH, Wright TC, Sharma A, Wright TL, Behrens CM. Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a subanalysis of the ATHENA study. *Lancet Oncol*. 2011;12:880−890.
29. Rijkaart DC, Berkhof J, Rozendaal L, et al. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. *Lancet Oncol*. 2012;13:78−88.
30. Murphy J, Kennedy EB, Dunn S, et al. HPV testing in primary cervical screening: a systematic review and meta-analysis. *J Obstet Gynaecol Can*. 2012;34:443−452.
31. Ronco G, Dillner J, Elfström KM, et al. Efficacy of HPV-based screening for prevention of invasive cervical cancer: follow-up of four European randomised controlled trials. *Lancet*. 2014;383:524−532.
32. Fontham ETH, Wolf AMD, Church TR, et al. Cervical cancer screening for individuals at average risk: 2020 guideline update from the American Cancer Society. *CA Cancer J Clin*. 2020;70:321−346.
33. Curry SJ, Krist AH, Owens DK, et al. Screening for cervical cancer us preventive services task force recommendation statement. *JAMA*. 2018;320:674−686.
34. Ogilvie GS, Van Niekerk D, Krajden M, et al. Effect of screening with primary cervical HPV testing vs cytology testing on high-grade cervical intraepithelial neoplasia at 48 months: the HPV FOCAL randomized clinical trial. *JAMA*. 2018;320:43−52.
35. Sawaya GF, Kerlikowske K, Lee NC, Gildengorin G, Washington AE. Frequency of cervical smear abnormalities within 3 years of normal cytology. *Obstet Gynecol*. 2000;96:219−223.
36. Boersma P, Black LI. Human papillomavirus vaccination among adults aged 18-26, 2013-2018. *NCHS Data Brief*. 2020;354:1−8.
37. Walker TY, Elam-Evans LD, Yankey D, et al. National, regional, state, and selected local area vaccination coverage among adolescents aged 13−17 years—United States, 2018. *MMWR Morb Mortal Wkly Rep*. 2019;68:718−723.
38. Palmer T, Wallace L, Pollock KG, et al. Prevalence of cervical disease at age 20 after immunisation with bivalent HPV vaccine at age 12-13 in Scotland: retrospective population study. *BMJ*. 2019;365.
39. Brotherton JML. The remarkable impact of bivalent HPV vaccine in Scotland. *BMJ*. 2019;365.
40. Castle PE, Xie X, Xue X, et al. Impact of human papillomavirus vaccination on the clinical meaning of cervical screening results. *Prev Med (Baltimore)*. 2019;118:44−50.
41. Odronic SI, Roberson J, Booth CN. Current practice patterns in nongynecologic and fine-needle aspiration cytology. *J Am Soc Cytopathol*. 2015;4:239−245.
42. Renshaw AA, Elsheikh TM. Sensitivity and workload for manual and automated gynecologic screening: best current estimates. *Diagn Cytopathol*. 2011;39:647−650.
43. Renshaw AA, Elsheikh TM. Predicting screening sensitivity from workload in gynecologic cytology: a review. *Diagn Cytopathol*. 2011;39:832−836.
44. Elsheikh TM, Austin RM, Chhieng DF, Miller FS, Moriarty AT, Renshaw AA. American Society of Cytopathology workload recommendations for automated Pap test screening: developed by the productivity and quality assurance in the era of automated screening task force. *Diagn Cytopathol*. 2013;41:174−178.
45. Davey DD. Amended reports: when, if ever? *Diagn Cytopathol*. 1997;17:399−400.