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# Evaluating the Use of LAST 2-Tiered Nomenclature and Its Impact on Reporting Cervical Lesions in a Population-Based Cancer Registry

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## Abstract

**Background:** Since 2012, the Lower Anogenital Squamous Terminology (LAST) Project recommended a 2-tiered nomenclature, low-grade and high-grade squamous intraepithelial lesion (LSIL and HSIL), to replace the 3-tiered cervical intraepithelial neoplasia (CIN) system for HPV-associated lesions. Prior to 2019, preinvasive cervical lesions classified as CIN3, severe dysplasia, carcinoma in situ (CIS), and adenocarcinoma in situ (AIS) were considered reportable to the Louisiana Tumor Registry for a CIN3 project funded by the Centers for Disease Control and Prevention (CDC); but lesions classified exclusively as high-grade/HSIL based on the 2-tiered system were not considered reportable. Due to the terminology changes, we wanted to know whether pre-2019 reportable criteria need to be modified to capture all reportable precancerous cervical cases diagnosed in 2019 forward.

**Objectives:** To evaluate the utilization of LAST 2-tiered classification, low-grade and high-grade squamous intraepithelial lesion, and p16 immunohistochemistry (IHC) testing on cervical biopsy/surgical specimens, assess the search criteria needed to identify high-grade lesions for the CDC-funded CIN3 project, and assess the impact of underreporting cervical lesions caused by terminology changes.

**Methods:** An equal number of abnormal/precancerous and normal cervical findings from biopsy pathology reports received in 2015 were randomly selected by an artificial intelligence (AI) search engine developed by Artificial Intelligence in Medicine Inc (AIM) using pre-2019 search criteria.

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Louisiana Tumor Registry (LTR) is authorized by law to collect all cancer-related data from medical records including pathology reports. The LTR is also mandated to conduct cancer studies. Data analyzed and presented in this manuscript was of sufficient sample size and both deidentified and aggregated. We received IRB approval (#5274 – Title "Data analysis of Louisiana Tumor Registry Analytic Data File") from the Louisiana State University Health Sciences Center- New Orleans to use LTR data for this study.

Selected pathology reports were reflagged for the reportability by AIM audit software based on 2019 search criteria and manually reviewed for the use of reportable terms including CIN3, severe dysplasia, CIS, AIS, high-grade/HSIL terminology, and CIN2 or CIN2–3 with positive p16 IHC testing. Cohen's kappa statistic was used to assess the agreement between AIM auto-coding and manual review. Positive predictive values (PPV) and sensitivity tests were computed to evaluate the reportable terms.

**Results:** Six out of 9 surveyed laboratories used 2-tiered terminology on cervical biopsy pathology reports and 7 performed p16 IHC tests. Of 1,974 randomly selected reports from 5 laboratories, 987 were flagged as precancer by AI using pre-2019 search criteria. After adding the high-grade/HSIL term into pre-2019 search criteria, precancerous reports increased by 29%. After manual review, 41.6% of these cases were reportable precancerous cervical cases with a PPV of 0.65 (95% CI, 0.62–0.67) and 13.6% had p16 IHC performed.

**Conclusions:** Both the 2-tiered and 3-tiered nomenclature are needed to ensure complete identification of all reportable high-grade cervical lesions.

### Keywords

cervical intraepithelial neoplasia; cervical precancer; high-grade; p16 IHC staining; squamous intraepithelial lesions

## Introduction

The main risk factor for acquiring precancerous cervical lesions is human papillomavirus (HPV) infection and over 95% of cervical neoplasia are HPV-related worldwide.[1–4] In 2006, the US Food and Drug Administration licensed the HPV vaccine for use in females aged 9 to 26 years.[5] Findings from the HPV-IMPACT study showed significantly decreased incidence rates of high-grade cervical intraepithelial neoplasia (CIN2–CIN3) and carcinoma in situ (CIS) among women aged 18 to 29 years after HPV vaccine introduction.[6] Due to increased understanding of HPV molecular biology and cervical carcinogenesis association, and apparent subjectivity when differentiating CIN2 and CIN3, the Lower Anogenital Squamous Terminology (LAST) Standardization Project, which was cosponsored by the College of American Pathologists and American Society for Colposcopy and Cervical Pathology, recommended the 2-tiered classification system, low-grade squamous intraepithelial lesions (LSIL) and high-grade squamous intraepithelial lesions (HSIL), for reporting histopathology from biopsies of all lower anogenital tract HPV-related squamous lesions in 2012.[7] This 2-tiered system was also endorsed by the World Health Organization (WHO) because it was more biologically relevant and more histologically reproducible than the 3-tiered CIN1 (mild dysplasia), CIN2 (moderate dysplasia), and CIN3 (severe dysplasia) system.[8] The LSILs are usually HPV infections that are self-limited, while the HSILs may progress to invasive carcinoma. Additionally, the LAST Standardization Project proposed use of p16 immunohistochemistry (IHC) staining to classify equivocal lesions into either LSIL if negative staining or HSIL if positive.[7]

Before 1996, CIN3, CIS, and adenocarcinoma in situ (AIS) of the cervix were reportable to central cancer registries in the United States; however, these cervical lesions were no longer

required to be collected and reported to the nation in 1996. In order to assess the association of HPV vaccination with precancerous cervical lesions in statewide populations, the Centers for Disease Control and Prevention (CDC) funded 4 central cancer registries, including the Louisiana Tumor Registry (LTR), to collect preinvasive cases diagnosed in 2009 and onward.[9] The eligible precancerous cervical lesions diagnosed before 2019 for this CDC-funded CIN3 project included CIN3, severe dysplasia, CIS, and AIS, and over 93% of cases were diagnosed either as CIN3 or severe dysplasia in Louisiana. Pathology reports containing the high grade or HSIL terminology were not initially considered reportable unless CIN3/severe dysplasia/CIS terminology was also documented. If pathologists solely used the 2-tiered LSIL/HSIL classification for cervical precancers since 2012, then the pre-2019 eligibility criteria, which is currently being used to define reportable cervical precancers for the CIN3 project, would not have captured all eligible cases diagnosed in 2012 and after.

To help address these issues, the LTR conducted an audit on cervical pathology reports in 2018 to evaluate use of the 2-tiered classification and p16 IHC test. The study objectives were to: (1) survey pathology laboratory results to determine use of the 2-tiered nomenclature when classifying precancerous cervical lesions; (2) evaluate information in pathology reports on recommended p16 IHC testing; (3) assess the additional search criteria needed when screening pathology reports to identify eligible cervical precancers diagnosed in 2019 and after; and (4) measure the impact of underreporting caused by terminology changes on reportable cervical precancers.

## Materials and Methods

### Data Source

Electronic pathology (e-path) reports received in 2015 for patients residing in Louisiana were used to conduct this audit. Only pathology reports from cervical biopsy specimens or specimens obtained from surgical procedures—including electrocautery, ablative and excisional procedures, endocervical curettage, loop electrocautery excision procedure, and hysterectomy—were included. This CDC-funded project was interested in the histopathologically confirmed CIN3 cases only; therefore, cytology reports were excluded. Louisiana state law authorizes LTR to collect all cancer-related data from medical records, including pathology reports, and conduct research. We received institutional review board (IRB) approval from the Louisiana State University Health Sciences Center—New Orleans to use LTR data for this study.

### Surveying Pathology Laboratories

Ten pathology laboratories, including 2 national laboratories with a high volume of precancerous cervical cases in Louisiana, were invited to participate in this study. These laboratories use either Artificial Intelligence in Medicine, Inc (AIM) developed E-path Reporter or the CDC-provided Public Health Information Network Messaging System (PHIN-MS) for their e-path reporting. Three questions, along with subquestions related to the use of 2-tiered terminology and molecular testing, were developed (Table 1). The survey was conducted via phone interviews.

## Defining Search Criteria and Eligible Cases

The search criteria are used to identify potential cervical precancers from pathology reports. All possible diagnosis terms related to precancerous cervical lesions were included in the search criteria. Prior to 2019, the search criteria (pre-2019 search criteria) included *International Classification of Diseases for Oncology*, 3rd edition (ICD-O-3) topography codes C53.0–C53.9, microscopically confirmed with the following terms: CIN3, CIS, AIS, grade 3, any in situ epithelial tumors, and/or severe dysplasia documented from cervical biopsy/surgical specimens. The new search criteria for 2019 include pre-2019 search criteria plus the following new terminologies: high-grade, high-grade squamous intraepithelial lesions (HSIL or HGSIL), CIN2, CIN2–3, CIN2/3, and/or p16 IHC test with cervix.

The eligible cases (or reportable cases) for pre-2019 are CIN3, severe dysplasia, CIS, and AIS. For 2019, the eligible cases include pre-2019 eligible cases plus precancers diagnosed based on the following reportable terms: HSIL, high-grade, and CIN2 or CIN2–3 with positive p16 IHC staining. Eligibility/search criteria and reportable terms for precancerous cervical lesions diagnosed before 2019 and in 2019 are summarized in Figure 1.

## System Used to Perform Audit

We used a standalone pathology report audit software developed by AIM to perform this audit. This system uses natural language processing (NLP) to interpret the content of pathology reports based on the provided terminologies (search criteria) and the artificial intelligence (AI) engines perform content coding and report selection. Search criteria were programmed into AIM audit system to flag potentially eligible cervical precancers from pathology reports for manual review. Eligible cases and reportable terms identified through manual review were entered into the AIM audit software.

## Sampling Pathology Reports

Five laboratories that used the AIM E-path Reporter were chosen for this audit. Pathology reports from 2015 with a cervical specimen from a biopsy or surgical procedure were included in the sample selection. AIM audit software randomly selected an equal number of abnormal/precancerous pathology reports based on pre-2019 search criteria and normal pathology reports (without eligible terms) with a maximum of up to 500 total cervical pathology reports per laboratory. For laboratories that had fewer than 250 cervical precancerous reports, we selected all of them and matched them with the same number of normal pathology reports. Pathology reports with precancer findings (cases) were flagged by AIM audit software if any of the pre-2019 search terms were documented in the free text of pathology reports. Flagged normal reports were those that did not meet the pre-2019 search criteria. After randomly selecting precancerous and normal reports based on the pre-2019 search criteria, the 2019 search criteria were implemented into AIM audit software to reanalyze and reflag these selected pathology reports to either precancerous reports or normal reports for manual review. Figure 2 shows the flow diagram of the audit process.

## Manual Review Processing

Pathology reports with either a precancerous or normal finding identified by AIM software were reviewed by a clinician and/or a certified tumor registrar who had extensive experience

reading pathology reports. These manual reviews were conducted in order to determine which pathology reports met pre-2019 and 2019 reportable terms for eligible cases. The reportable precancerous terms were recorded for each eligible case and then were categorized into 3 terminology subgroups: pre-2019 reportable terms only (CIN3, CIS, severe dysplasia, and AIS), new reportable terms only (HSIL, high-grade, and CIN2 or CIN2–3 with positive p16 IHC staining), and the combination (2019 reportable terms). The presence of p16 IHC testing and the subsequent results of p16 IHC staining were collected and coded. CIN2 and CIN2/3 without high-grade term, without p16 IHC test performed, or with negative p16 test were not considered reportable as precancer for this project. Cervical precancerous lesions identified solely based on Papanicolaou (Pap) test reports, with previous invasive cervical cancer, or followed by an invasive cervical cancer within 12 months were not reportable and excluded.

### p16 Immunohistochemistry Staining and Test Results

We developed 5 different codes to classify p16 IHC staining status and result: *test not performed*, *negative*, *positive*, *indeterminate*, and *unknown test result*. The indeterminate category was used when we were unable to determine whether the p16 IHC test was positive or negative based on terms in the pathology report. The positive test result was used when the pathology report described p16 staining as block-positive (strong and diffuse block staining), full-thickness staining of the squamous epithelium or strong nuclear and cytoplasmic staining of the basal mucosa with extension to at least one-third of epithelial thickness. The negative test result was applied to cases in which p16 staining was reported as weak, focal, patchy, cytoplasmic only, or staining confined to only basal layer.

### Statistical Analysis

The frequency distributions including the proportions of reportable terminologies were generated for reportable cervical precancers by pathology laboratory. We also calculated the percentages of pathology reports with the p16 IHC test performed by the laboratory. We used Cohen's kappa statistic to assess the agreement between AIM and manual review. The positive predictive value (PPV) and negative predictive value (NPV) as well as sensitivity and specificity based on AIM's selection versus manual review (as the reference standard) were computed to assess the predictability and degree of discrepancy for reportability. Finally, the $\chi^2$ test was used to assess the association between p16 IHC testing and terminology group. Data analysis was carried out using SAS v 9.4 (SAS Institute, Inc).

## Results

Nine out of 10 laboratories participated in our survey. Six laboratories used the 2-tiered terminology on cervical biopsy pathology reports and the remaining laboratories used it for cytology reports (Pap test) only (Table 1). Of the 6 laboratories that used the 2-tiered terminology, 5 of them used it in combination with CIN terminology. Seven laboratories performed p16 IHC tests and 5 of them also performed Ki-67 tests. All laboratories that reported using p16 IHC and Ki-67 testing included test results in their pathology reports even if this testing was not done in house.

Five pathology laboratories, which cover 51% of Louisiana's annual case count for reportable precancerous cervical lesions and use both 2-tiered and CIN 3-tiered terms, were included in the audit. A total of 1,974 pathology reports (987 abnormal/precancerous reports and 987 normal reports) were randomly selected by AIM audit software based on pre-2019 search criteria from these laboratories. After implementing 2019 search criteria into AIM audit software, 1,273 previously selected pathology reports were flagged as precancer cases, which increased the number of potential reportable cases for manual review by 29 %. After manual review, 822 (41.6%) reports met 2019 reportable criteria (combination of pre-2019 and new reportable terms). The percentage of agreement was 77.2% with a kappa statistic of 0.56 (95% CI, 0.53–0.60), moderate agreement, and a PPV of 0.65 (95% CI, 0.62–0.67). The estimated NPV was 1.00 (95% CI, 0.995–1.000), which indicated all normal reports flagged by AIM were nonreportable. The sensitivity for correctly identifying reportable cases was 1.0 (95% CI, 0.996–1.000); however, the specificity was low at 0.61 (95% CI, 0.58–0.64).

Of 822 eligible cases identified through manual review, 129 (15.7%) contained pre-2019 reportable terms only, 347 (42.2%) were solely based on the new reportable terms, and 346 (42.1%) included both pre-2019 and new reportable terms (Figure 3). Including new reportable terms for precancerous cervical lesions resulted in a 73% increase in reportable cases. Pathology laboratories varied in their use of reportable terminologies, ranging from 3.9%–49.1% based on the pre-2019 terms only, 19.3%–47.3% based on new reportable terms only, and 27.7%–54.9% based on 2019 reportable terms (both pre-2019 and new terms) in pathology reports.

Table 2 presents the frequency distribution of usage of reportable terminology by pathology laboratory. In general, the most frequently used terms were HSIL (or HGSIL) (59.3%) followed by CIN3 (49.5%) and high-grade (46.7%). Laboratory #5 used the "HSIL" term in the majority (93.1%) of their reportable pathology reports and laboratory #2 favored using "high-grade" (Table 2). About 6.5% of reportable cases had CIN2–3 with a positive p16 test and 5.8% had CIN2 with a positive p16 result in pathology reports. We further examined those 347 reportable cases identified from new reportable terms only; all of them except 1 (identified through positive p16 IHC for CIN2–3) had either HSIL or high-grade terminology documented in the pathology report and 19.6% only included the HSIL/high-grade terminology without the CIN terminology (Figure 4). Additionally, of 346 reportable cases containing a combination of terms, 90.1% were CIN3 with HSIL/high-grade combination.

Among audited pathology reports, 268 (13.6%) had p16 IHC staining performed and 71.3% of these had positive staining (Table 3). Use of p16 IHC staining by laboratory ranged from 0% to 26.6% (Table 3) and it was also significantly associated with type of terminology group ($P < .0001$) (Figure 5). Precancerous cervical lesions identified solely through the new reportable terminology had a higher percentage of p16 tests performed (36.9%) than those identified through pre-2019 terminology (6.9%) or using a combination of term (15.9%).

## Discussion

Population-based cancer registries use the cervical biopsy pathology report as the main data source for timely collecting reportable cervical precancers. Due to the change in pathologists' practices for documenting HPV-associated precancerous cervical lesions and the increasing use of the 2-tiered terminology, reporting of cervical precancers using only the CIN designation led to underreporting of high-grade lesions by population-based cancer registries since 2012. The new eligibility criteria (2019 criteria) for precancerous cervical lesions, implemented through the AIM audit software, had a sensitivity of 100%, which most likely did not omit any reportable pathology reports. Yet, by using the new eligibility criteria, there was a tradeoff of low specificity (61%) which 39% of nonreportable cases were flagged as reportable for manual review.

While all 5 selected laboratories reported using both CIN 3-tiered and LAST and WHO recommended 2-tiered terminology systems in their cervical histopathology reports, some pathologists could use either 2-tiered or CIN terminology alone to classify cervical lesions in biopsy pathology reports. Our audit found the use of 2-tiered system varied by laboratories. Overall, 84.1% of reportable pathology reports received in 2015 contained the high-grade or HSIL terms with range from 50.9% to 96.1%. Although we did not collect information on 2-tiered system usage by pathologists, the findings from a single large academic pathology practice showed the variation of increasing use of HSIL in cervical biopsy specimens before and after the implementation of 2-tiered terminology among pathologists. The range of differences in increasing 2-tiered system use were from 0.1% to 9.6%.[10]

It is well recognized that the diagnosis of cervical pathology using the CIN 3-tiered classification is subjective and varies by pathologist, especially in CIN2 cases.[11–14] Several studies have shown the low interobserver reproducibility of the CIN2 distinction in both cervical cytologic and histologic interpretations, and using histopathologic criteria alone without a molecular biomarker to differentiate CIN2, may not be reliable.[14–20] The use of p16 IHC tests on cervical biopsy specimens has been demonstrated to improve the accuracy of CIN diagnosis and to assist in differentiating precancer from a mimic of precancer. If the LAST recommendations were followed, estimated overall use of p16 IHC staining would be about 20% to 25% of all cervical biopsies.[7] In our audit, 2 out of 5 audited laboratories used p16 IHC test, close to the percentage estimated by the LAST Project (18.6% and 26.6%). The average was 13.6%, which was comparable with a previous study that found 13.9%.[10] Additionally, compared with reportable cervical precancer reports containing the CIN3 terms (pre-2019 reportable terms) only, those using high-grade terms were most likely to order a p16 IHC test (6.9% vs. 36.9%). This result implies that pathology laboratories using the 2-tiered system are also following the LAST's recommendation to use a p16 IHC test to clarify any category considered intermediate for a cervical biopsy specimen.

By adding new reportable terms (HSIL/high-grade and CIN2 or CIN2–3 with positive p16 IHC test), eligible precancerous cervical cases diagnosed in 2015 increased 73% when compared with using pre-2019 reportable terms. In order to align with the current practice and be able to compare data collected before 2019 and after, the 2019 reportable terms include pre-2019 and new reportable terms. For the HSIL/high grade category, additional

CIN terminologies will be collected. When only the HSIL/high grade terminology was documented without CIN terminology or other pre-2019 reportable terms, this will be noted in the data collection as well.

A major limitation of collecting data on high-grade cervical precancers is that changing pathological terminology can make it difficult to estimate a reliable incidence rate for precancerous cervical lesions. In general, the estimated incidence rate of HPV-related cervical intraepithelial neoplasia has been commonly presented as low-grade neoplasia (CIN1) and high-grade neoplasia (CIN2, CIN3).[21,22]A report that was able to estimate incidence rates for each CIN category used data collected from the New Mexico HPV Pap Registry, the only United States registry that captures individual CIN categories from 2007 to 2014.[23] When precancerous cases determined solely based on “high-grade” terminology, this prevents researchers from studying that specific CIN category. However, this issue can be resolved if pathologists add CIN nomenclature with the basic 2-tiered classification for histopathology reports that would help to distinguish CIN2 and CIN3 from HSIL. Another limitation is that the interpretation of p16 IHC staining results in the pathology report is based on a pathologist’s experience and can be subjective.

In conclusion, findings from this audit helped to define the new eligibility criteria for reportable precancerous cervical cases for the CDC-funded CIN3 project, as well as highlighted the 2-tiered and 3-tiered nomenclature needed to ensure complete identification of all cervical precancer cases. Population-based cancer registries collecting cervical precancers should modify their reporting criteria to incorporate expert recommendations and terminology used in current practice and reporting by pathologists to ensure complete cervical precancer ascertainment in their catchment area. Most importantly, federal cancer organizations need to partner with the College of American Pathologists to provide pathologists the training and educational opportunities regarding the terminology changes and uses when reporting cervical precancers to avoid underreporting.

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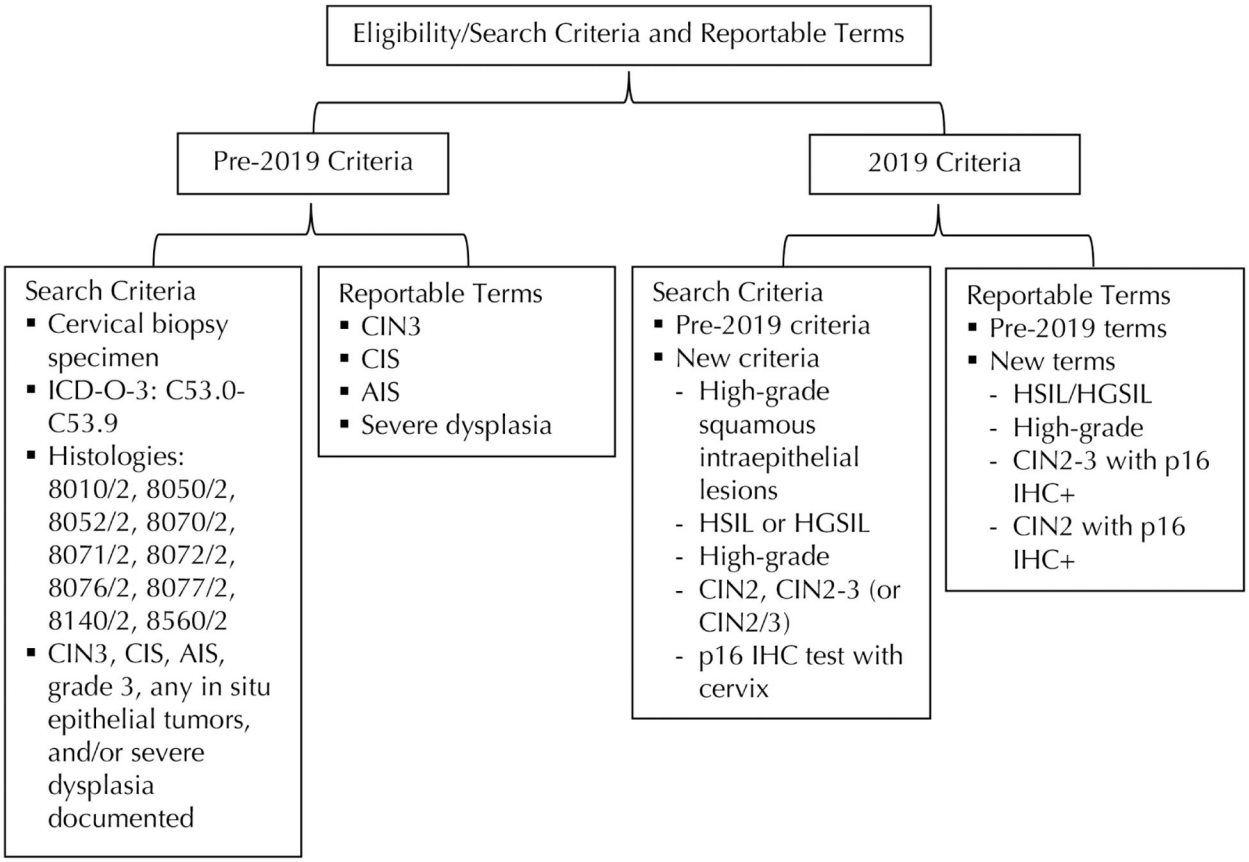


**Figure1. Eligibility/Search Criteria and Reportable Terms for Precancerous Cervical Lesions**

AIS, adenocarcinoma in situ; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; CIN2–3, cervical intraepithelial neoplasia grade 2 or 3; CIS, carcinoma in situ; HSIL (HGSIL), high-grade squamous intraepithelial lesion; ICD-O-3, *International Classification of Disease for Oncology*, 3rd edition; IHC, immunohistochemistry.

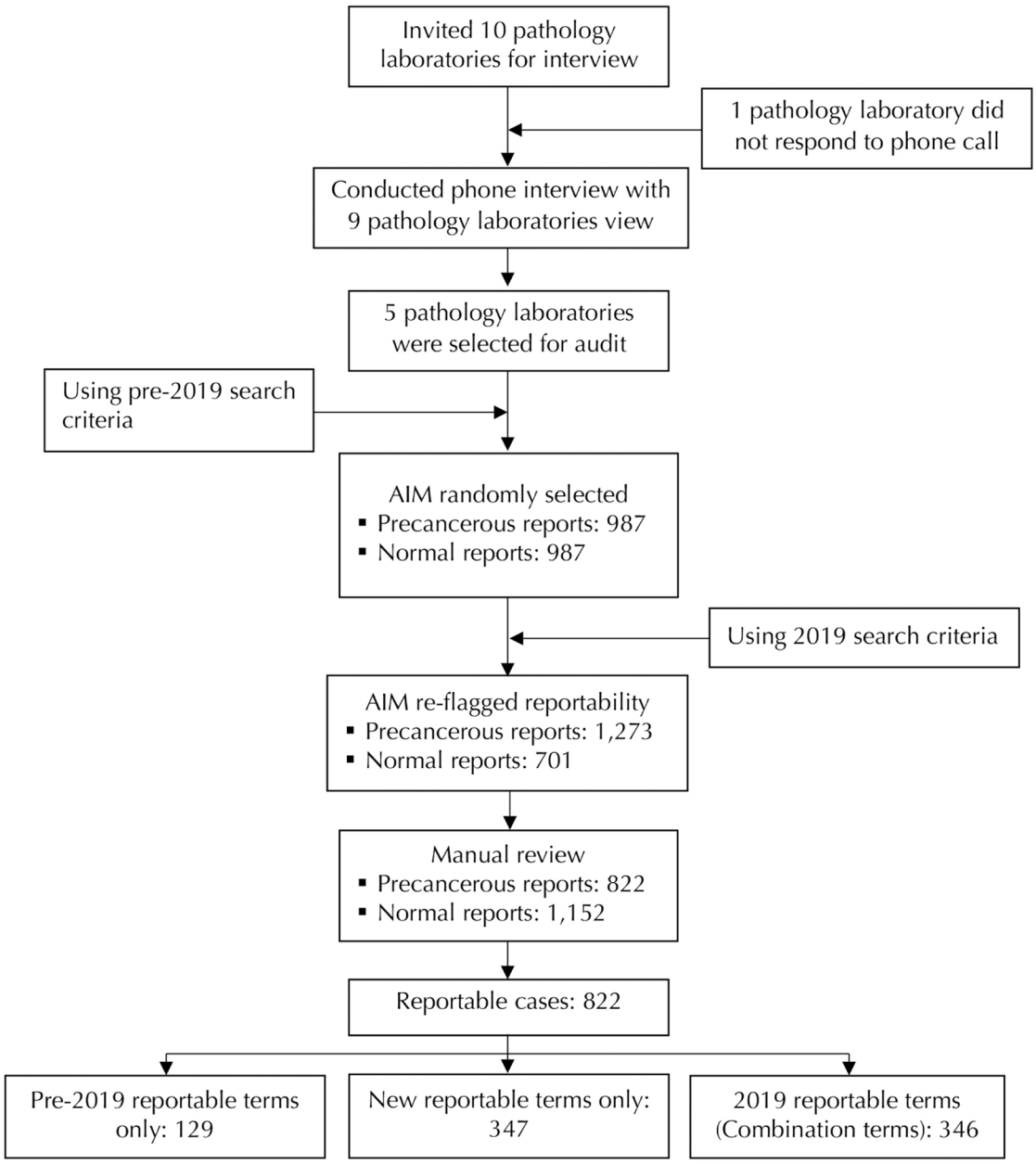


**Figure 2. Audit Processing for Precancerous Cervical Lesions**

AIS, adenocarcinoma in situ; AIM, Artificial Intelligence in Medicine Inc; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; CIN2–3, cervical intraepithelial neoplasia grade 2 or 3; CIS, carcinoma in situ; HSIL (HGSIL), high-grade squamous intraepithelial lesion; IHC, immunohistochemistry.

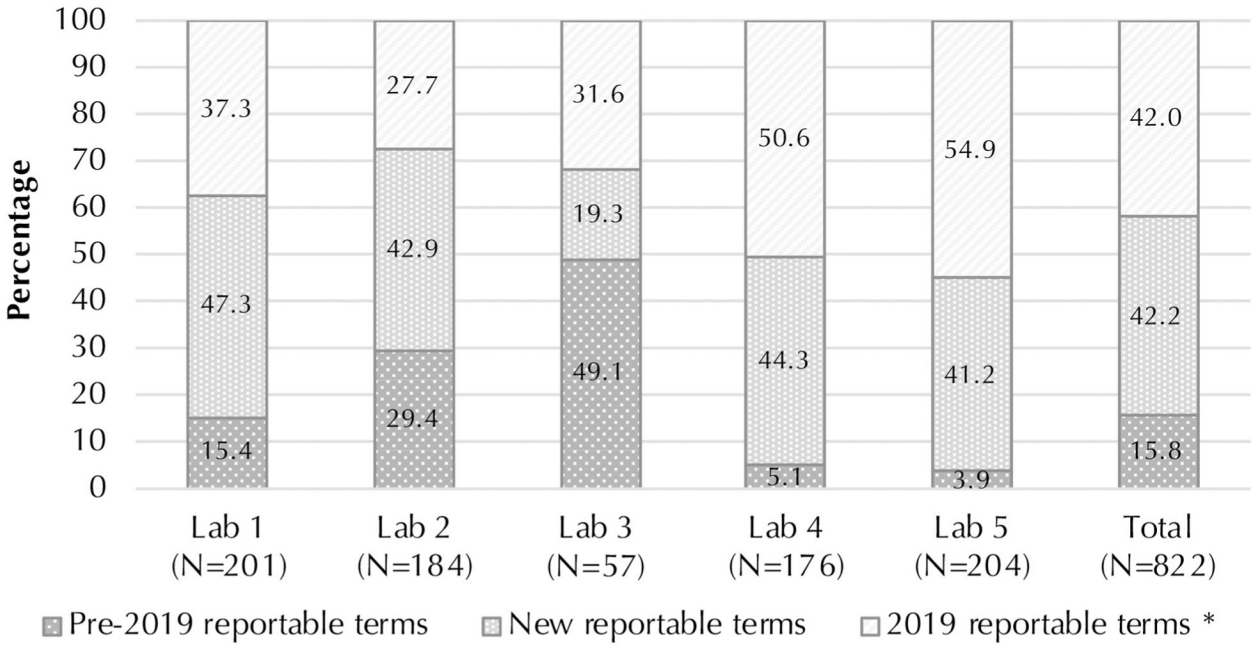


**Figure 3. Use of Reportable Terms Identified in 2015 Pathology Reports by Selected Pathology Laboratories in Louisiana**

* Contained both pre-2019 (CIN3, severe dysplasia, CIS, and AIS) and new reportable terms (high-grade, HSIL, and CIN2 or CIN2–3 with positive p16 IHC test).

AIS, adenocarcinoma in situ; CIN2, cervical intraepithelial neoplasia grade 2; CIN2–3, cervical intraepithelial neoplasia grade 2 or 3; CIS, carcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; IHC, immunohistochemistry.

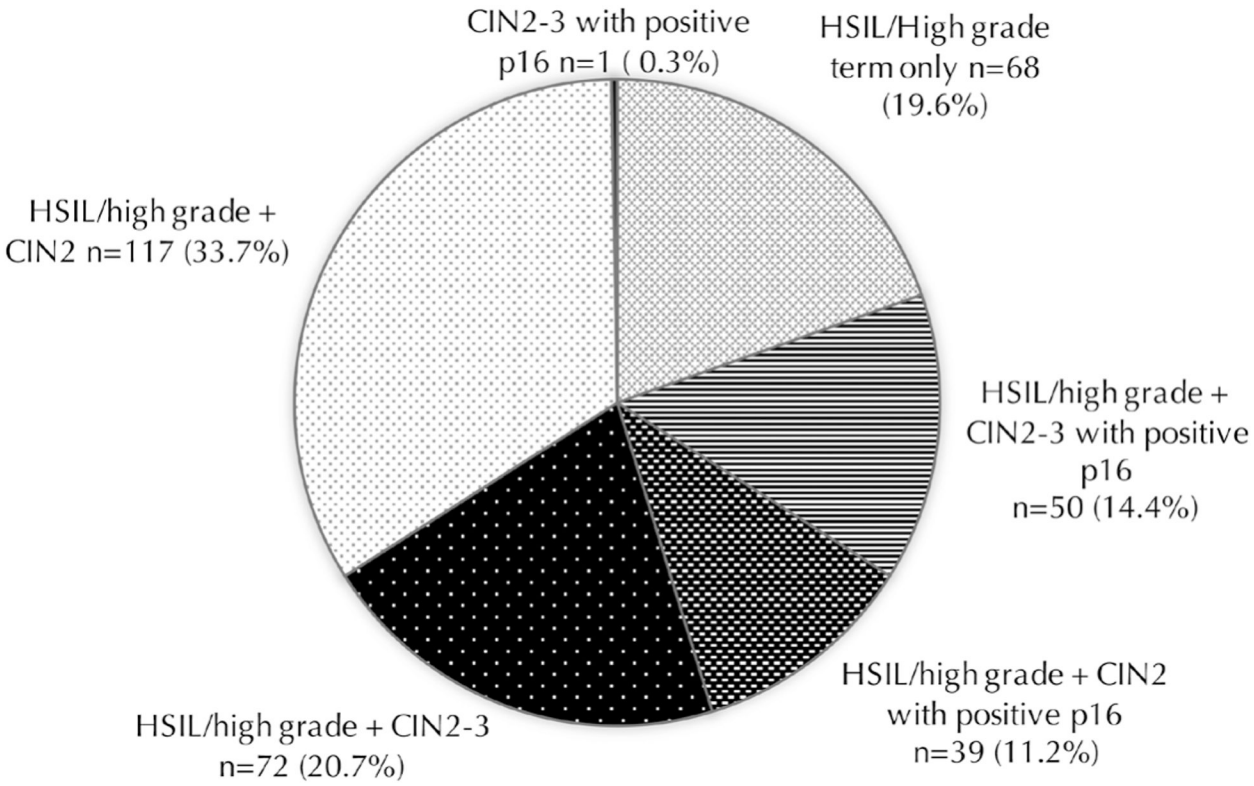


**Figure 4. Distribution of Reportable High-Grade Preinvasive Cervical Cases Based on New Eligibility Terms (n = 347)**

CIN2, cervical intraepithelial neoplasia grade 2; CIN2–3, cervical intraepithelial neoplasia grade 2 or 3; HSIL, high-grade squamous intraepithelial lesion.

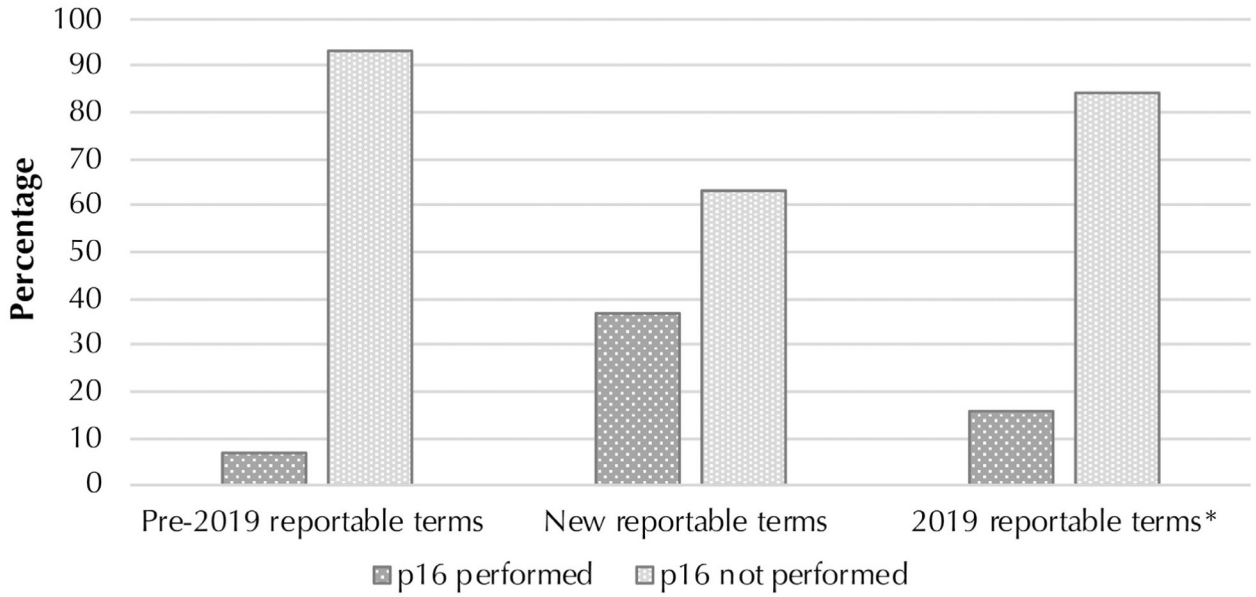


**Figure 5. Proportion of p16 IHC Testing Status by Type of Terminology Group**

* Contained both pre-2019 (CIN3, severe dysplasia, CIS, and AIS) and new reportable terms (high-grade, HSIL, and CIN2 or CIN2–3 with positive p16 IHC test).

AIS, adenocarcinoma in situ; CIN2, cervical intraepithelial neoplasia grade 2; CIN2–3, cervical intraepithelial neoplasia grade 2 or 3; CIS, carcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; IHC, immunohistochemistry.

**Table 1.**

Survey Questions about Use of Lower Anogenital Squamous Terminology (LAST), 2-Tiered Classification, in Cervical Biopsy Specimen Based on 9 Laboratories

| *Survey Questions* | *Responses* | |
|---|---|---|
| | **Yes** | **No** |
| 1. Are pathologists using the recommended LAST 2-tiered terminology (HSIL/LSIL) on biopsy reports? | 6 | 3 |
| 1a. Do pathologists also document the CIN2 or CIN3 classification in addition to the LAST terminology in the pathology reports? | 5 | 1 |
| 2. Are pathologists performing p16 IHC staining for CIN2 cases? | 7 | 2 |
| 2a. If so, is this done in house? | 7 | 0 |
| 2b. Is p16 available on pathology report? | 7 | 0 |
| 3. Are pathologists performing Ki-67 (grading), ProEx C or other IHC staining either alone or in combination with p16 IHC staining for CIN2 cases? | 5 | 4 |
| 3a. If so, what type? | Ki-67 | NA |
| 3b. Is Ki-67 or ProEx C or other IHC available on pathology report? | 5 | 0 |

CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; HSIL, high-grade squamous intraepithelial lesion; IHC, immunohistochemistry; LSIL, low-grade squamous intraepithelial lesion.

**Table 2.**

Frequency Distribution of Reportable Terminology by Pathology Laboratory

| *Terminology* | *Lab 1 (n = 201)* | *Lab 2 (n = 184)* | *Lab 3 (n = 57)* | *Lab 4 (n = 176)* | *Lab 5 (n = 204)* | *Total (n = 822)* | *Contained Pre-2019 Terms (n = 475)* | *Based on New Terms Only (n = 347)* |
|---|---|---|---|---|---|---|---|---|
| | **Count (%)** | **Count (%)** | **Count (%)** | **Count (%)** | **Count (%)** | **Count (%)** | **Count (%)** | **Count (%)** |
| 1.AIS | 2 (1.0) | 0 (0.0) | 2 (3.5) | 0 (0.0) | 11 (5.4) | 15 (1.8) | 15 (3.2) | 0 |
| 2. CIN3 | 81 (40.3) | 93 (50.5) | 43 (75.4) | 83 (47.2) | 107 (54.5) | 407 (49.5) | 407 (85.7) | 0 |
| 3. CIS | 9 (4.5) | 11 (6.0) | 0 (0.0) | 0 (0.0) | 4 (2.0) | 24 (2.9) | 24 (5.1) | 0 |
| 4. Severe dysplasia | 18 (9.0) | 1 (0.5) | 1 (1.8) | 15 (8.5) | 2 (1.0) | 37 (4.5) | 37 (7.8) | 0 |
| 5. HSIL | 107 (53.2) | 53 (28.8) | 25 (43.9) | 112 (63.6) | 190 (93.1) | 487 (59.3) | 278 (58.5) | 209 (60.2) |
| 6. High grade | 104 (51.7) | 101 (54.9) | 13 (22.8) | 126 (71.6) | 40 (19.6) | 384 (46.7) | 170 (35.8) | 214 (61.7) |
| 7. CIN2–3 with p16+ | 29 (14.4) | | 0 (0.0) | 21 (11.9) | 2 (1.0) | 53 (6.5) | 5 (1.1) | 51 (14.7) |
| 8. CIN2 with p16+ | 14 (7.0) | 20 (10.9) | 0 (0.0) | 8 (4.6) | 6 (2.9) | 48 (5.8) | 7 (1.5) | 41 (11.8) |

AIS, adenocarcinoma in situ; CIN2, cervical intraepithelial neoplasia grade 2; CIN3, cervical intraepithelial neoplasia grade 3; CIN2–3, cervical intraepithelial neoplasia grade 2 or 3; CIS, carcinoma in situ; HSIL, high-grade squamous intraepithelial lesion; lab, laboratory.

**Table 3.**

Frequency Distribution of p16 Immunohistochemistry (IHC) Staining Performed Status and Test Result by Pathology Laboratory

| *p16 IHC staining* | *Lab 1 (n = 500)* | *Lab 2 (n = 464)* | *Lab 3 (n = 134)* | *Lab 4 (n = 376)* | *Lab 5 (n = 500)* | *Total (n = 1974)* |
|---|---|---|---|---|---|---|
| | **Count (%)** | **Count (%)** | **Count (%)** | **Count (%)** | **Count (%)** | **Count (%)** |
| Performed | 93 (18.6) | 49 (10.6) | 0 | 100 (26.6) | 26 (5.2) | 268 (13.6) |
| Negative | 27 (29.0) | 17 (34.7) | 0 | 17 (17.0) | 5 (19.2) | 66 (24.6) |
| Positive | 58 (62.4) | 31 (63.3) | 0 | 81 (81.0) | 21 (80.8) | 191 (71.3) |
| Indeterminate | 6 (6.5) | 0 | 0 | 2 (2.0) | 0 | 8 (3.0) |
| Unknown | 2 (2.2) | 1 (2.0) | 0 | 0 | 0 | 3 (1.1) |
| Not performed | 407 (81.4) | 415 (89.5) | 134 (100.0) | 276 (73.4) | 474 (94.8) | 1,706 (86.4) |

IHC, immunohistochemistry; lab, laboratory.