

## Review of outside pathology prior to treatment of cervical intraepithelial neoplasia: a cost analysis

Heather R. Williams MD,<sup>1</sup> Alison C. Agner MD,<sup>2</sup> Colleen K. Stockdale MD, MS<sup>3</sup>

Keywords: Cervical dysplasia, cervical intraepithelial neoplasia, cervical pathology, pathology review, cost analysis

### Abstract

**Objectives:** Academic institutions routinely require in-house review of pathology prior to treatment. However, it is unclear if pathology review is beneficial for the management of patients referred for cervical intraepithelial neoplasia (CIN). This study aims to determine if review of outside pathology for CIN at an academic medical center resulted in a change in the treatment plan and the associated cost for pathology review.

**Methods:** A retrospective chart review of patients referred for treatment of CIN, including review of outside cytology and histology was performed from January 1 to December 31, 2007 after obtaining IRB approval. Data was analyzed to determine whether pathology diagnosis was changed from the outside facility interpretation; classified as minor if there was no change in clinical management and major if there was a change in treatment as a result of the internal review. Demographic and pathology information was collected from electronic medical records. Billing information was collected from the finance department. Data were analyzed using descriptive statistics.

**Results:** Seventy-eight patients were identified of which 54 had outside pathology slides available for pathology review. Eleven had a

minor change in the pathology diagnosis (20%). None of the changes in pathology diagnosis resulted in a change in treatment plan (major). The total pathology review charge was \$14,679 for the 54 patients, with an average charge per patient of \$272. Nine of the cases were charged twice to reflect the opinion of two separate pathologists (internal consultation). Of the 54 patients, 23 (43%) had state supported insurance, 24 (44%) had private insurance, and 7 (13%) were self-pay. A total of \$12,969.29 was not covered/paid (88% of all charges) and thus absorbed by the institution.

**Conclusion:** Mandatory review of outside pathology is a common practice. However, it may not be beneficial in all clinical situations. While this pathology review for CIN resulted in minor changes for 20% of patients referred to our academic/tertiary institution, it did not affect any treatment recommendations. Pathology review did increase the cost burden to the institution and the patient.

<sup>1</sup>Medical College of Georgia at Augusta University, Department of Obstetrics and Gynecology, Augusta, GA

<sup>2</sup>Colorado Permanente Medical Group Obstetrics, Denver, CO

<sup>3</sup>Department of Obstetrics and Gynecology, University of Iowa Hospitals and Clinics, Iowa City, IA

Please cite this paper as: Williams HR, Agner AC, Stockdale CK. Review of outside pathology prior to treatment of cervical intraepithelial neoplasia: a cost analysis. POG in Press. 2018 March; Article 2 [ 7 p.]. Available from: [http://ir.uiowa.edu/pog\\_in\\_press/](http://ir.uiowa.edu/pog_in_press/). Free full text article.

**Corresponding author:** Colleen Stockdale, MD, MS, Department of Obstetrics and Gynecology, 200 Hawkins Drive, Iowa City, IA 52246, Phone: 319-384-6849, Fax: 319-384-8620. Email: [colleen-stockdale@uiowa.edu](mailto:colleen-stockdale@uiowa.edu)

**Financial Disclosure:** The authors report no conflict of interest.

Copyright: © 2018 Williams et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

## **Introduction**

It is estimated that over 300,000 women in the United States have a diagnosis of cervical intraepithelial neoplasia (CIN) II-III, the precursor to cervical cancer.<sup>1</sup> The annual incidence of CIN II-III is estimated at 1.5 per 1000 women annually.<sup>2-3</sup> Overall, the risk of progression of CIN II lesions to cancer is around 5% and the risk of progression to CIN III is 20%.<sup>4</sup> A diagnosis of CIN III however, carries a 12% risk of progression to cancer. Another factor to consider is the cost of treatment. In one study, the costs per episode of care were higher for CIN II-III than CIN I (\$1,634 vs \$1,084) with an estimated annual burden per 1,000 US women of \$1,803 for CIN II-III.<sup>2</sup>

Patients with CIN II-III lesions are often referred to tertiary/academic care centers for treatment. A survey of 126 hospitals found 50% required internal review of outside slide material before surgical intervention, while 75% of academic institutions required in-house review of outside pathology.<sup>5</sup> The goal of this secondary review was reduction in error by redundancy. A 21 month review at The Johns Hopkins Hospital found the rate of major diagnostic disagreement ranged from 1 to 3% across all organ sites.<sup>6</sup> Reviews of gynecologic oncology patients have found 4.7 to 6.8% of cases resulted in a change in diagnosis that had major prognostic implications.<sup>7-8</sup> Regarding CIN II-III specifically, most of the variability in diagnosis seems to stem from the diagnosis of CIN II. This is due to the heterogeneity of CIN II lesions and discrepancies between different pathologists.<sup>9</sup> This is clinically important because the threshold for treatment is CIN II, with exceptions for management

in younger women.<sup>10-11</sup>

The largest study to identify variability in pathology between clinical pathologists and academic pathologists was a multicenter randomized control trial, the ASCUS-LSIL Triage Study (ALTS).<sup>12</sup> They found that interpretation of CIN I by the clinical center was corroborated by the quality control group in only 42.6% biopsies.<sup>12</sup> Alternatively, an equal proportion of originally diagnosed CIN I biopsies (41.0%) were interpreted as negative by the pathology quality control group. Indeed, interpathologist variability regarding the diagnosis of CIN has been identified in multiple studies.<sup>13</sup>

The purpose of this study was to determine if review of outside pathology at an academic medical center resulted in a difference in the diagnosis and subsequent treatment plan for women referred with CIN, and explore the cost associated with the secondary pathology review.

## **Materials and Methods**

Participants of this retrospective cohort review included all women age 18 years of age or older who were referred to a single academic/tertiary colposcopy clinic for evaluation and treatment of cervical high-grade dysplasia, including CIN II and CIN III from January 1, 2007 to December 31, 2007. University of Iowa Institutional Review Board approval was obtained. Exclusion criteria included missing outside material (pathology slides) available for pathology review.

Demographic characteristics including age, parity, contraception use, menopausal status, tobacco use, as well as the external pathology diagnosis and

internal pathology review were abstracted from electronic patient records. Non-cervical gynecologic pathology was excluded, including vulvar and vaginal pap smears as well as endometrial biopsies. The patient payer status, amount charged for pathology review of outside material, and amount covered by insurance was collected from the billing department. The cost for pathology review was in

2007 dollars (actual cost during the time period of the retrospective review).

Data were analyzed using descriptive statistics including frequency, means and percentages. Diagnostic discrepancies were categorized as minor or major as described by others.<sup>7,14</sup> Minor discrepancies did not impact clinical care and major discrepancies resulted in a change in treatment.<sup>7,14</sup>

**Table 1: Patient demographic characteristics**

Patient Characteristics	% Respondents	
Median Age (years):	21 (Range 18-78)	
Parity:	0	49%
	1 or greater	31%
	Unknown	20%
Menopause status:	Pre:	94%
	Post:	6%
Tobacco Use:	Yes	26%
	No	52%
	Unknown	22%
Contraception:	Pregnant	6%
	None	11%
	Unknown	9%
	DepoProvera	22%
	OCP	38%
	Condoms	2%
	Surgical	6%
	Menopause	6%

**Results**

A total of 78 patients were referred for treatment of CIN II-III from outside our

institution, of which 54 had complete information (including outside pathology slides for review) available for analysis. The median age of patients in the study

was 21 years with a range of 18-78 years. Forty-nine percent were nulliparous and 94% were premenopausal. Fifty-two percent denied tobacco use. The most commonly reported form of birth control was oral contraceptives (38%) followed by medroxyprogesterone injection (22%). (Table 1)

The internal pathology review resulted in a change of diagnosis for 11 of the 54 cases (20%). Of which 5 of 11 (45%) were upgraded from CIN II to CIN III and 6 of 11 (55%) were downgraded from CIN III to CIN II. None of the pathology reviews resulted in a change in treatment plan. – the recommendation for treatment was based on treatment of high grade lesions (encompassing CIN II/III) and the pathology reviews did not change from high grade to low grade or vice-versa.

The total amount charged for the internal pathology review was \$14,679 with the average charge per patient \$272 (\$228-470). Nine patients were charged between \$456-470 because two separate pathologists reviewed the outside slides (review with internal consultation). The insurance payers were evenly dispersed between Iowa Care (state form of Medicaid) and private insurance (43% vs 44%) with an average cost of \$6500 billed for the entire visit including pathology review, colposcopy, and treatment if it was performed.

Regarding the pathology review charge, the total amount captured by insurance was \$1,709 which left the remaining amount of \$12,969 (88%) uncovered, with the hospital absorbing the cost. Furthermore, among the uncovered charges, six patients did not present for

evaluation and treatment despite referral and pathology review, comprising \$1722 of the uncovered charges.

## **Discussion**

The introduction of cervical screening with cytology has significantly reduced morbidity and mortality related to cervical cancer in developed nations.<sup>15</sup> This is due to the detection of both pre-invasive changes as well as invasive cancer at earlier stages which allows for earlier treatment.<sup>15</sup> When abnormal cytology and histology is identified, patients may be referred to another facility for further evaluation and management. There is limited data to support or refute whether review of outside pathology for diagnostic confirmation is necessary or cost effective especially for CIN. One could argue that review of outside pathology prior to treatment would potentially guard against needless treatment of CIN. This is especially important in younger populations that desire fertility. In a study published in the Journal of the American Medical Society, treatment for CIN was not associated with increased risk of total preterm delivery or spontaneous preterm delivery but did reveal an increased risk of preterm premature rupture of membranes.<sup>16</sup> As noted previously, this is clinically relevant as CIN II is often the threshold for treatment and may present as a transient process especially in younger women.<sup>11-13</sup>

While our study demonstrated that up to 20% of cytology and pathology diagnoses were changed on review, none of the changes resulted in a modification of the treatment plan. A study recently published in the American Journal of Surgical Pathology found that

only 38.2% of CIN I and 38.0% of community-diagnosed CIN II were confirmed by expert review.<sup>13</sup> Community-diagnosed CIN I and CIN II were downgraded respectively to CIN I and upgraded to CIN II on panel review 35.1% and 32.4% of the time. They did find that more CIN II were upgraded to CIN III (53.3%) than CIN III being downgraded to CIN II (32.6%).<sup>13</sup> However, comparison of CIN II found the percent of the population diagnosed as CIN II by the community was only slightly greater than that estimated by expert review (11.9% vs. 10.7%,  $P=0.024$ ).<sup>13</sup> While heterogeneity in pathology diagnosis is reported, Chan et al. evaluated types of specimens reviewed among 569 pathology specimens at a tertiary care center and concluded cervical and vaginal smears do not benefit from pathology review.<sup>14</sup> Cytological specimens accounted for no major discrepancies.<sup>14</sup>

Our results did reveal significant cost added to each review with up to 88% of the charges unpaid. This adds to the enormous cost of human papillomavirus (HPV) related disease including CIN. In 2010, the overall direct cost burden of diagnosis and management of HPV-associated disease was estimated to be 8.0 billion dollars.<sup>17</sup> Approximately \$6.6 billion (82.3%) was for screening and associated follow-up.<sup>17</sup>

Our study is limited by the time period data were collected from. Given newer screening guidelines published in 2012, this same study conducted more recently might yield different results. Our study is subject to limitations in methodology including single institution retrospective cohort study with a small sample size. An attempt was made to extract data effectively from electronic

medical records. To limit selection bias, all patients with outside specimens were included. The small sample size is a limitation in that major discrepancies affecting management may have been identified if all patients referred for treatment had specimens available for review (54 of 78 had pathology material available for review). Further studies are needed to validate the results and to determine if there is a cost reduction achieved by avoiding a secondary pathology review for CIN. Additionally, given recent implementation of molecular pathology techniques to aid in the diagnosis of CIN II, it would be interesting to see if new techniques improve diagnostic accuracy and consistency among pathologists.

Based on the findings of this study, mandatory review of outside pathology prior to treatment of cervical intraepithelial neoplasia at a referral center may not necessarily be of value and should possibly be left to the clinical judgment of the treating physician.

## References

1. Saslow D, Castle PE, Cox JT, Davey DD, Einstein MH, Ferris DG, Goldie SJ, Harper DM, Kinney W, Moscicki AB, Noller KL, Wheeler CM, Ades T, Andrews KS, Doroshenk MK, Kahn KG, Schmidt C, Shafey O, Smith RA, Partridge EE; Gynecologic Cancer Advisory Group, Garcia F. American Cancer Society Guideline for human papillomavirus (HPV) vaccine use to prevent cervical cancer and its precursors. *CA Cancer J Clin.* 2007 Jan-Feb;57(1):7-28.  
<https://doi.org/10.3322/canjclin.57.1.7>  
PubMed PMID: 17237032.

2. Henk HJ, Insinga RP, Singhal PK, Darkow T. Incidence and costs of cervical intraepithelial neoplasia in a US commercially insured population. *J Low Genit Tract Dis.* 2010 Jan;14(1):29-36. <https://doi.org/10.1097/LGT.0b013e3181ac05e9> PubMed PMID: 20040833.
3. Insinga RP, Glass AG, Rush BB. Diagnoses and outcomes in cervical cancer screening: a population-based study. *Am J Obstet Gynecol.* 2004 Jul;191(1):105-13. <https://doi.org/10.1016/j.ajog.2004.01.043> PubMed PMID: 15295350.
4. Nasiell K, Nasiell M, Vačlavinková V. Behavior of moderate cervical dysplasia during long-term follow-up. *Obstet Gynecol.* 1983 May;61(5):609-14. PubMed PMID: 6835614.
5. Gupta D, Layfield LJ. Prevalence of inter-institutional anatomic pathology slide review: a survey of current practice. *Am J Surg Pathol.* 2000 Feb;24(2):280-4. <https://doi.org/10.1097/00000478-200002000-00014> PubMed PMID: 10680896.
6. Kronz JD, Westra WH, Epstein JI. Mandatory second opinion surgical pathology at a large referral hospital. *Cancer.* 1999 Dec 1;86(11):2426-35. [https://doi.org/10.1002/\(SICI\)1097-0142\(19991201\)86:11<2426::AID-CNCR34>3.0.CO;2-3](https://doi.org/10.1002/(SICI)1097-0142(19991201)86:11<2426::AID-CNCR34>3.0.CO;2-3) PubMed PMID: 10590387.
7. Eskander RN, Baruah J, Nayak R, Brueseke T, Ji T, Wardeh R, Tewari KS. Outside slide review in gynecologic oncology: impact on patient care and treatment. *Int J Gynecol Pathol.* 2013 May;32(3):293-8. <https://doi.org/10.1097/PGP.0b013e31826739c4> PubMed PMID: 23518913.
8. Selman AE, Niemann TH, Fowler JM, Copeland LJ. Quality assurance of second opinion pathology in gynecologic oncology. *Obstet Gynecol.* 1999 Aug;94(2):302-6. [https://doi.org/10.1016/S0029-7844\(99\)00318-X](https://doi.org/10.1016/S0029-7844(99)00318-X) PubMed PMID: 10432147.
9. Dalla Palma P, Giorgi Rossi P, Collina G, Buccoliero AM, Ghiringhello B, Gilioli E, Onnis GL, Aldovini D, Galanti G, Casadei G, Aldi M, Gomes VV, Giubilato P, Ronco G; NTCC Pathology Group. The reproducibility of CIN diagnoses among different pathologists: data from histology reviews from a multicenter randomized study. *Am J Clin Pathol.* 2009 Jul;132(1):125-32. [https://doi.org/10.1309/AJCPBRK7D1YI\\_UWFP](https://doi.org/10.1309/AJCPBRK7D1YI_UWFP) PubMed PMID: 19864243.
10. Kinney W, Hunt WC, Dinkelspiel H, Robertson M, Cuzick J, Wheeler CM; New Mexico HPV Pap Registry Steering Committee. Cervical excisional treatment of young women: a population-based study. *Gynecol Oncol.* 2014 Mar;132(3):628-35. <https://doi.org/10.1016/j.ygyno.2013.12.037> Epub 2014 Jan 4. PubMed PMID: 24395062; PubMed Central PMCID: PMC3992337.
11. Massad LS, Einstein MH, Huh WK, Katki HA, Kinney WK, Schiffman M, Solomon D, Wentzensen N, Lawson HW; 2012 ASCCP Consensus Guidelines Conference. 2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. *J Low Genit Tract Dis.* 2013 Apr;17(5 Suppl 1):S1-S27. <https://doi.org/10.1097/LGT.0b013e318287d329> Erratum in: *J Low Genit Tract Dis.* 2013 Jul;17(3):367. PubMed PMID: 23519301.

12. Stoler MH, Schiffman M; Atypical Squamous Cells of Undetermined Significance-Low-grade Squamous Intraepithelial Lesion Triage Study (ALTS) Group. Interobserver reproducibility of cervical cytologic and histologic interpretations: realistic estimates from the ASCUS-LSIL Triage Study. *JAMA*. 2001 Mar 21;285(11):1500-5.  
<https://doi.org/10.1001/jama.285.11.1500>  
PubMed PMID: 11255427.
13. Stoler MH, Ronnett BM, Joste NE, Hunt WC, Cuzick J, Wheeler CM; New Mexico HPV Pap Registry Steering Committee. The Interpretive Variability of Cervical Biopsies and Its Relationship to HPV Status. *Am J Surg Pathol*. 2015 Jun;39(6):729-36.  
<https://doi.org/10.1097/PAS.00000000000000381>  
PubMed PMID: 25602796; PubMed Central PMCID: PMC4428379.
14. Chan YM, Cheung AN, Cheng DK, Ng TY, Ngan HY, Wong LC. Pathology slide review in gynecologic oncology: routine or selective? *Gynecol Oncol*. 1999 Nov;75(2):267-71.  
<https://doi.org/10.1006/gyno.1999.5567>  
PubMed PMID: 10525384.
15. Saslow D, Solomon D, Lawson HW, Killackey M, Kulasingam SL, Cain J, Garcia FA, Moriarty AT, Waxman AG, Wilbur DC, Wentzensen N, Downs LS Jr, Spitzer M, Moscicki AB, Franco EL, Stoler MH, Schiffman M, Castle PE, Myers ER; American Cancer Society; American Society for Colposcopy and Cervical Pathology; American Society for Clinical Pathology. American Cancer Society, American Society for Colposcopy and Cervical Pathology, and American Society for Clinical Pathology screening guidelines for the prevention and early detection of cervical cancer. *Am J Clin Pathol*. 2012 Apr;137(4):516-42.  
<https://doi.org/10.1309/AJCPTGD94EVRSJCG>  
PubMed PMID: 22431528.
16. Sadler L, Saftlas A, Wang W, Exeter M, Whittaker J, McCowan L. Treatment for cervical intraepithelial neoplasia and risk of preterm delivery. *JAMA*. 2004 May 5;291(17):2100-6.  
<https://doi.org/10.1001/jama.291.17.2100>  
PubMed PMID: 15126438.
17. Chesson HW, Ekwueme DU, Saraiya M, Watson M, Lowy DR, Markowitz LE. Estimates of the annual direct medical costs of the prevention and treatment of disease associated with human papillomavirus in the United States. *Vaccine*. 2012 Sep 14;30(42):6016-9.  
<https://doi.org/10.1016/j.vaccine.2012.07.056>  
Epub 2012 Aug 4. PubMed PMID: 22867718.