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## An Evaluation by Midwives and Gynecologists of Treatability of Cervical Lesions by Cryotherapy Among Human Papillomavirus–Positive Women

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### Abstract

**Objectives**—To estimate efficacy of a visual triage of human papillomavirus (HPV)–positive women to either immediate cryotherapy or referral if not treatable (eg, invasive cancer, large precancers).

**Methods**—We evaluated visual triage in the HPV-positive women aged 25 to 55 years from the 10,000-woman Guanacaste Cohort Study (n = 552). Twelve Peruvian midwives and 5 international gynecologists assessed treatability by cryotherapy using digitized high-resolution cervical images taken at enrollment. The reference standard of treatability was determined by 2 lead gynecologists from the entire 7-year follow-up of the women. Women diagnosed with histologic cervical intraepithelial neoplasia grade 2 or worse or 5-year persistence of carcinogenic HPV infection were defined as needing treatment.

**Results**—Midwives and gynecologists judged 30.8% and 41.2% of women not treatable by cryotherapy, respectively ( $P < 0.01$ ). Among 149 women needing treatment, midwives and gynecologists correctly identified 57.5% and 63.8% ( $P = 0.07$  for difference) of 71 women judged not treatable by the lead gynecologists and 77.6% and 59.7% ( $P < 0.01$  for difference) of 78 women judged treatable by cryotherapy. The proportion of women judged not treatable by a reviewer varied widely and ranged from 18.6% to 61.1%. Interrater agreement was poor with mean pairwise overall agreement of 71.4% and 66.3% and  $\kappa$ 's of 0.33 and 0.30 for midwives and gynecologists, respectively.

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**Conclusions**—In future “screen-and-treat” cervical cancer prevention programs using HPV testing and cryotherapy, practitioners will visually triage HPV-positive women. The suboptimal performance of visual triage suggests that screen-and-treat programs using cryotherapy might be insufficient for treating precancerous lesions. Improved, low-technology triage methods and/or improved safe and low-technology treatment options are needed.

### Keywords

Cervical intraepithelial neoplasia; Cryotherapy; Screen-and-treat; Human papillomavirus; Low-resource settings

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A portable, low-cost, rapid test for carcinogenic types of human papillomavirus (HPV), a necessary but not sufficient cause of cervical cancer, has been developed for low-resource areas and is currently being pilot tested.<sup>1</sup> The new HPV test might be sensitive enough to test women once or twice in their lifetime if administered past young adulthood, when women are at greatest risk for persistent HPV infection associated with the treatable conditions of cervical intraepithelial neoplasia grades 2 and 3 (CIN2 and CIN3). Currently, the only widely available treatment option that is suitable for such a screen-and-treat strategy is cryotherapy, the standard, safe, low-technology method for treating precancerous lesions. In a screen-and-treat program, women in the targeted age group found to be infected with carcinogenic types of HPV (HPV positive) would receive immediate cryotherapy.

A crucial problem with such a program is the inability of cryotherapy to treat women with invasive cancer and risk of failure in the presence of large or deep HPV-associated lesions and some benign abnormalities such as polyps, severe atrophy, or a distorted cervix. In addition, cryotherapy is not recommended when the squamocolumnar junction on the cervix extends into the endocervical canal, thereby precluding exclusion of cancer diagnosis. Therefore, as suggested by previous research, a large minority of women found to be HPV positive in low-resource settings and needing treatment to prevent cancer might not actually be treatable by cryotherapy.<sup>2–4</sup> We do not know whether practitioners will be able to determine which women are in fact treatable.

In the context of a screen-and-treat program, local health providers will need to use a visual inspection with acetic acid (VIA) examination of the cervix to determine which HPV-positive women are eligible for immediate cryotherapy. Visual inspection with acetic acid is not an accurate diagnostic tool. However, we propose a new application of VIA called “visual triage.” This visual triage uses simpler criteria to identify women as either treatable or not treatable by cryotherapy after HPV testing. In this context, VIA is not meant to detect precancerous lesions, which has been the focus of previous research,<sup>5–7</sup> but rather distinguishes whether abnormalities are treatable with cryotherapy.

The goal of this study was to determine how well primary-level practitioners, specifically midwives, could triage HPV-positive women to cryotherapy versus advanced care. Because studies have reported conflicting results when comparing the accuracy of non-physicians and physicians to visually inspect the cervix,<sup>7–8</sup> we also examined and compared midwife performance with that of gynecologists. In addition, several studies suggest that low-level (4.5×) magnification does not influence the accuracy of VIA to detect precancerous lesions,<sup>9–10</sup> a hypothesis we explored.

### METHODS

To determine how multiple examiners triaged women from the same study population, we distributed digitized, high-resolution cervical photographs taken at enrollment into the

population-based Proyecto Epidemiológico Guanacaste (PEG). Evaluation of these kinds of images (at least when evaluated by expert colposcopists) has been shown to be comparable to real-time colposcopy in prediction of CIN2+ histology.<sup>11</sup> We included nonhysterectomized, nonpregnant women aged 25 to 55 years who tested positive the day of enrollment for any 1 of 14 carcinogenic HPV types by polymerase chain reaction methods (types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 66, and 68). The level of analytical sensitivity of the new test is slightly less than that of HC2 (Qiagen, Gaithersburg, Md), which performs similarly to consensus primer polymerase chain reaction methods.<sup>12</sup> Proyecto Epidemiológico Guanacaste was a natural history study of HPV enrolling more than 10,000 women in 1993 to 1994 with the approval of the National Cancer Institute and Costa Rican institutional review boards. Detailed methods of recruitment, screening, and follow-up are published elsewhere.<sup>3,13-14</sup>

Reviewers consisted of 12 midwives practicing in San Martín, Perú, with extensive training in VIA from a previous project<sup>15</sup> and 5 gynecologists from 4 developing countries with experience using cryotherapy. Midwives received a 1-day, in-person orientation (J.C.G., J.J.), and gynecologists individually reviewed the protocol and spoke with lead authors (J.C.G., J.J.). Reviewers evaluated static cervical images from HPV-positive women using a bilingual (English/Spanish), Internet-based evaluation tool developed collaboratively by the National Library of Medicine and the National Cancer Institute.<sup>16</sup> The processing of the original photographic images (Cervigrams) in PEG to produce optimally compressed and digitized images suitable for Internet distribution is detailed elsewhere.<sup>17</sup>

Using the evaluation tool, midwife and gynecologist reviewers answered if the image was adequate for evaluation and judged whether, if confronted with the patient at enrollment, they would have considered her immediately treatable by cryotherapy. Reviewers based their decision on whether the enrollment images showed a condition contraindicated for cryotherapy. They also knew her age and that she was HPV positive and not pregnant. For women deemed not treatable by cryotherapy, reviewers selected 1 or more of the following reasons: suspected invasive cancer, large dysplastic lesion, lesion in the cervical canal, lesion in the vaginal fornix, entire squamocolumnar junction not visible, presence of polyp(s), severe cervical atrophy, vaginal wall close to the cervix, cervical distortion, or large ectropion. The protocol specified that women were treatable if they had large ectopy so long as there was no evidence of dysplasia and the squamocolumnar junction could be completely covered by 2 applications of cryotherapy.

Midwives conducted evaluations at 2 Internet cafes and gynecologists at their workplace or home. Most monitors were cathode ray tube between 15 and 17 inches standardized to 6500-K color temperature when possible. Reviewers were encouraged to visualize cervical images through a tube or rolled-up dark folder to reduce screen glare. Cases were presented in a randomized sequence at each log-in. A time stamp recorded the speed of their decision (up to 10 minutes allowed). Each evaluation was immediately stored in a database at the National Library of Medicine in Bethesda, Md, and reviewers could not change their evaluation.

To better replicate an in vivo visual triage examination, images were generated for each monitor and resolution to measure 8.9 × 6.1 cm. After evaluating all small images, reviewers were presented with large images (30.5 × 20.8 cm). Finally, reviewers evaluated an additional 50 small and 50 large images randomly selected for each reviewer. For 2 reviewers, a slow Internet connection necessitated that they access the images from a DVD or CD rather than the Internet.

Analyses were performed using SAS 9.1.3 analytic software (SAS Institute Inc, Cary, NC). We estimated the proportions of women judged treatable by cryotherapy by various categories, and the influence of participant characteristics on whether the woman was judged treatable, by using logistic regression. We could not use simple statistics because more than 1 reviewer

evaluated each image; we accounted for possible “autocorrelation” within images by fitting the logistic regression models using generalized estimating equations,<sup>18</sup> leaving unconstrained the correlation of judgments for any pair of reviewers. The intraobserver reliability for each reviewer’s additional 50 small and 50 large images and interobserver reliability for 66 pairs of midwives and 10 pairs of gynecologists were calculated by considering pairwise agreement and unweighted  $\kappa$  statistics.

We judged whether each woman needed treatment at the time of enrollment when the baseline HPV test and visual image were taken. Although the need for treatment referred to the time of enrollment, we were able to judge the truth of each woman’s baseline condition and risk of cancer based on the entire PEG clinical record, defined as “disease status at exit.” A woman was considered to require treatment at baseline if she was diagnosed with CIN2+ by histology at baseline or during PEG follow-up or had a carcinogenic type of HPV infection that persisted to her cohort exit visit. We required at least 5 or more years of follow-up for persistence. A woman was judged not to require treatment if she was negative at exit (at least 5 years later) for the carcinogenic HPV type(s) found at enrollment infection and therefore was not at appreciable risk of cancer.

The reference standard of treatability by cryotherapy was a consensus evaluation of the entire PEG clinical record by 2 lead reviewers (J.J., F.G.) from a previous analysis.<sup>3</sup> In that analysis, they used all cytology, histology, images, and HPV typing from each woman’s multiple visits in PEG to determine whether cryotherapy at enrollment would have likely cured a precancerous lesion or persistent HPV infection. For example, women with a normal-appearing cervix at enrollment would have been determined not treatable by cryotherapy if their subsequent clinical record showed an invasive cancer diagnosed a few years later or lesion subsequently found in the endocervical canal. In addition, there were benign conditions (eg, polyp, severe atrophy, or a distorted cervix) for which cryotherapy was contraindicated.

## RESULTS

At enrollment in PEG, 559 nonhysterectomized women aged 25 to 55 years were HPV positive. Of 552 women with a readable cervical image from enrollment, PEG clinical review showed that 121 (21.9%) had CIN2+ (80 were diagnosed at enrollment and 41 during follow-up, diagnosed 3.3 years later, on average). By PEG study exit, an average of 6.7 years after enrollment, 28 (5.1%) had a type-specific HPV infection that was persistent, and 403 (73.0%) cleared their HPV infection therefore not requiring treatment because they were not at appreciable risk of cervical cancer.

Compared with gynecologists, midwives judged fewer women to be not treatable by cryotherapy, requiring referral instead (30.8% and 41.2%, respectively;  $P < 0.01$  for difference) (Table 1). Women were significantly more likely to be judged not treatable by cryotherapy (see  $P$  for trends in Table 1) if they had conditions associated with a less visible transformation zone (older age, no oral contraceptive use, low parity, and postmenopausal status) or disease requiring treatment at study exit based on PEG clinical record review. With the exception of disease status at exit and extent of ectopy, these associations were attenuated, but not eliminated, after adjusting for study participant’s age, most likely reflecting changes in the position of the squamocolumnar junction. When evaluating large images instead of small images, both midwives and gynecologists judged fewer women as not treatable, declining from 30.8% to 26.4% ( $P < 0.01$ ) for midwives and from 41.2% to 34.7% ( $P < 0.01$ ) for gynecologists, respectively.

We found substantial variability among reviewers. The proportion of women judged not treatable by a reviewer ranged from 18.6% to 61.1%. This wide range translated to poor inter-

observer reliability with overall agreement at 71.4% and 66.3% and poor  $\kappa$  values of 0.33 and 0.30 for midwives and gynecologists, respectively (Table 2). As expected, reviewers' agreement with themselves was better than with each other, with higher overall agreement of 80.0% and 78.0% for midwives and gynecologists and moderate  $\kappa$  of 0.51 for both types of reviewers. For gynecologists, magnification slightly improved intraobserver but not interobserver agreement.

The frequency with which midwives and gynecologists selected reasons why a woman was not treatable varied (Table 3). Gynecologists were more likely to identify technical reasons for not being treatable: a large lesion, a distorted cervix, large ectopy, or vaginal wall close to the cervix, whereas midwives were more likely to cite a lesion that extended into the canal.

Table 4 compares the average triage screening performance of gynecologists and midwives, with determinations of treatability by the consensus evaluation of 2 lead reviewers based on all clinical records and cervical images.<sup>3</sup> The presentation is restricted to the most important group, that is, those women requiring treatment for subsequent CIN2+ or persistent HPV infection based on PEG clinical records. As already shown in Table 1, gynecologists were overall more likely than midwives to judge women to be untreatable. The same tendency was evident in Table 4 after stratification by lead reviewer evaluation and need for treatment.

Among 71 women who required treatment and were judged by lead reviewers to not be treatable by cryotherapy, the gynecologists were slightly more likely than midwives to agree with lead reviewers (63.8% vs 57.5%;  $P = 0.07$ ) (Table 4). Magnification did not significantly change these proportions (data not shown). In this group of women who were judged to be untreatable and in need of referral, women aged 40 to 55 years were more likely to be correctly identified as untreatable compared with those aged 25 to 39 years (75.3% vs 57.4% [ $P = 0.02$ ] for gynecologists and 65.7% vs 53.1% [ $P = 0.13$ ] for midwives).

Of 78 women who required treatment and were judged by lead reviewers to be treatable by cryotherapy, midwives were more likely than gynecologists to agree with lead reviewers (77.6% vs 59.7%;  $P < 0.01$ ). Magnification increased this proportion correctly judged treatable to 81.6% ( $P = 0.07$ ) and 71.9% ( $P < 0.01$ ) for midwives and gynecologists, respectively. No age associations with agreement were observed among these 78 women.

Variability among reviewers in general tendency to consider women treatable or not translated into predictable and wide differences in the practitioners' individual agreement with lead reviewers. Those practitioners who correctly identified a high percentage of women judged by the lead reviewers to be not treatable tended to identify a low percentage of women judged to be treatable, and vice versa (data not shown).

## DISCUSSION

These results have several possible programmatic implications for the influence of practitioner training on visual triage and utility of magnification in visual triage. A primary problem, as previously reported, is that many women are not treatable by cryotherapy.<sup>3</sup> Even in the perfect setting where all patients had a colposcopy examination, which in itself is not perfect, many women requiring treatment would have not been treatable by cryotherapy.

In this analysis, we assessed an added level of complexity, evaluating the performance of visual triage among midwives and gynecologists, and found it to differ by reviewer training as well as by individual practitioner. Gynecologists were less likely to judge women treatable by cryotherapy, and among 62 cases where all gynecologists agreed a woman was not treatable, still 69.4% of midwives judged them treatable. This difference could be explained by dissimilarity of practice settings and extent of disease. Because midwives in the San Martín

region practice at a primary care level where advanced diagnostic and treatment options are not widely accessible, they might be less willing to withhold treatment unless absolutely necessary. In contrast, because gynecologists see referral patients where such procedures are readily available, they might be more inclined to refer a borderline case. Midwives and gynecologists also see different spectra of disease in their practices that can influence their threshold for referral. In screening programs, midwives most often evaluate women without disease and could be more likely to judge a woman as “normal.” Alternatively, gynecologists consult more severe cases in their referral practices and might be more likely to judge women as requiring advanced care.

Although low-level magnification increased the proportion of women judged treatable by cryotherapy, only gynecologists’ accuracy (compared with the lead reviewers) to correctly judge women treatable by cryotherapy significantly improved (perhaps because of a greater sense of security in judgment). Their agreement on woman judged not treatable by the lead reviewers did not improve, and the performance of midwives was not improved by magnification.

The implication of judging women not treatable by cryotherapy will depend on the health care setting. In a screening context where advanced care is readily available, more referrals might not present a burden for women or the health system. For settings where advanced care is not readily available, referring a woman who requires treatment and is treatable by cryotherapy would constitute failure to adequately manage that woman. In such contexts, an ability to detect women who can be cured by cryotherapy might be more desirable because women who are referred are at higher risk of not receiving care.<sup>4,19</sup>

The use of cervical images instead of in vivo evaluations might have resulted in poorer performance because the reviewers could not manipulate the cervix. However, studies elsewhere have documented that colposcopic impressions at the time of patient examination and subsequent review of digitized cervical images taken the same day are correlated and equivalent in (mediocre) reliability and accuracy for prediction of underlying precancerous lesions.<sup>11</sup> In addition, reliability between reviewers is a prerequisite for accuracy in this kind of clinical practice. That we found limited reliability when evaluating the same image a second time suggests that visual triage of HPV-positive women would be inaccurate.

For this analysis, we considered a woman to have persistent HPV infection requiring treatment if she had the same type-specific carcinogenic genotype of HPV at PEG study exit after at least 5 or more years of follow-up. Such a rigorous reference standard for disease would not be applicable in clinical practice as older women with a type-specific infection persisting after 6 months or 1 year are at higher risk for precancer and could be considered candidates for ablative, if not excisional, treatment.<sup>20</sup>

Our research cautions the ability of health practitioners to visually triage HPV-positive women to immediate cryotherapy versus referral for advanced care, especially among women most likely to fail cryotherapy. The possible utility and impact of a visual triage test should be incorporated into future calculations of the success or failure of a screen-and-treat program using HPV testing and cryotherapy.

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**TABLE 1**

Mean proportion of HPV-positive women judged not treatable by cryotherapy by midwives and gynecologists, stratified by women's characteristics

	Mean Proportion Judged Not Treatable*					
	Total		Midwives		Gynecologists	
	n	%	Mean	95% CI	Mean	95% CI
Total†	552	100	30.8	28.5–33.3	41.2	38.5–44.0
Age, y						
25–29	166	30.1	22.6	19.7–25.7	32.7	29.0–36.6
30–34	141	25.5	27.7	25.3–30.1	38.2	35.4–41.1
35–39	98	17.8	33.4	30.9–36.1	44.1	41.2–47.0
40–49	108	19.6	39.7	35.8–43.7	50.1	46.0–54.3
50–55	39	7.1	46.4	40.6–52.2	56.2	50.3–61.9
<i>P</i>			<0.01			<0.01
Oral contraceptive use						
Never	117	21.2	35.6	30.2–41.5	46.4	40.4–52.4
Former user	268	48.6	31.6	28.3–35.2	39.5	35.8–43.2
Current user	167	30.3	26.2	22.4–30.3	40.3	35.3–45.6
<i>P</i>			0.01			0.19
No. live births						
None	24	4.4	21.0	16.7–26.0	29.0	23.7–34.9
1–2	183	33.2	26.3	23.3–29.5	35.7	32.2–39.4
3–5	260	47.1	32.3	29.8–34.9	43.1	40.2–46.0
6+	85	15.4	39.0	34.2–44.0	50.8	45.5–56.1
<i>P</i>			<0.01			<0.01
Women reached menopause						
No	505	91.5	28.8	26.4–31.2	39.3	36.5–42.1
Yes	47	8.5	53.0	44.1–61.6	61.2	51.7–69.9
<i>P</i>			<0.01			<0.01
No. sexual partners						
1–2	350	71.4	29.2	26.3–32.2	39.4	36.1–42.8

	Mean Proportion Judged Not Treatable*					
	Total		Midwives		Gynecologists	
	n	%	Mean	95% CI	Mean	95% CI
3-4	102	20.8	32.8	29.2-36.5	42.9	38.8-47.1
5+	38	7.8	36.6	29.4-44.4	46.5	38.3-54.9
<i>P</i>			0.08		0.14	
Enrollment cytology						
Normal or reactive changes	318	57.6	27.8	24.9-30.9	40.1	36.6-43.8
ASCUS/ atypia	92	16.7	34.0	28.0-40.4	43.2	36.8-49.9
LSIL	71	12.9	29.3	23.5-35.9	39.0	32.2-46.2
HSIL+	71	12.9	41.9	34.9-49.1	45.5	37.9-53.3
<i>P</i>			<0.01		0.35	
Disease status at exit <sup>‡</sup>						
Did not require treatment <sup>§</sup>	403	73.0	27.8	25.2-30.5	37.4	34.4-40.5
Had disease requiring treatment <sup>  </sup>	149	27.0	39.1	34.3-44.2	51.5	45.9-57.0
<i>P</i>			<0.01		<0.01	
Extent of ectopy <sup>¶</sup>						
Normal	515	93.3	30.7	28.2-33.2	38.5	35.8-41.2
Large	37	6.7	33.3	25.0-42.7	78.7	69.3-85.8
<i>P</i>			0.57	28.2-33.2	<0.01	
Presence of inflammation on enrollment cytology						
No	352	63.7	27.8	24.2-31.6	40.6	36.2-45.3
Yes	200	36.2	32.6	29.6-35.7	41.5	38.2-44.9
<i>P</i>			0.05		0.76	

\* Mean proportion judged not treatable based on univariate logistic regression using generalized estimating equations to account for all reviewers examining the same images.

<sup>†</sup> Statistically significant difference between mean proportions judged not treatable by midwives and gynecologists ( $P < 0.01$ ).

<sup>‡</sup> Based on worst histology or HPV testing in PEG clinical record review.

<sup>§</sup> At study exit, women negative for the same HPV type(s) detected at enrollment.

<sup>||</sup> At study exit, women positive for the same HPV type(s) detected at enrollment and/or women diagnosed with CIN2+.

<sup>¶</sup> Determination made by lead reviewers during evaluation of enrollment cervical images.<sup>3</sup>

CI, Confidence interval; ASCUS, Atypical squamous cells of undetermined significance; LSIL, Low-grade squamous intraepithelial lesion; HSIL, High-grade squamous intraepithelial lesion.

**TABLE 2**

Midwives' and gynecologists' intraobserver and interobserver agreement of visual triage when evaluating small and large images

	Mean Pairwise Overall Agreement		Mean Pairwise $\kappa$	
	Small	Large	Small	Large
	Interobserver			
Midwives	71.4	74.4	0.33	0.35
Gynecologists	66.3	69.1	0.30	0.28
Intraobserver				
Midwives	80.0	82.0	0.51	0.53
Gynecologists	78.0	85.5	0.51	0.64

**TABLE 3**

Reasons why a woman was determined not treatable by midwives and gynecologists

	Midwives <sup>†</sup>	Gynecologists <sup>†</sup>	P <sup>‡</sup>
Any reason *	30.8%	41.2%	
Cannot visualize the squamocolumnar junction	13.3%	12.4%	0.23
Lesion in the canal	9.5%	3.9%	<0.01
Large lesion	2.2%	7.5%	<0.01
Suspected cancer	1.1%	2.7%	<0.01
Large ectopy	2.6%	8.7%	<0.01
Distorted cervix	3.4%	8.6%	<0.01
Severe atrophy	2.1%	2.0%	0.75
Lesion in the fornix	1.9%	2.4%	0.15
Polyp	1.2%	0.9%	0.28
Vaginal wall close to the cervix	1.8%	4.0%	<0.01

\* With the exception of suspicious cancer, women could have more than 1 reason.

<sup>†</sup> Midwives and gynecologists could select more than 1 reason.

<sup>‡</sup> Fisher exact test for difference in frequency between midwives and gynecologists.

**TABLE 4**

Among HPV-positive women who had disease requiring treatment, \* mean proportion judged not treatable by cryotherapy by midwives and gynecologists, given consensus evaluation of lead reviewers<sup>3</sup>

Had Disease Requiring Treatment <sup>†</sup>	Total (n = 149)	Consensus Evaluation of Lead Reviewers <sup>3</sup>	
		Not Treatable by Cryotherapy <sup>‡</sup> (n = 71)	Treatable by Cryotherapy <sup>‡</sup> (n = 78)
Midwife triage			
Not treatable by cryotherapy	39.1% (34.3–44.2)	57.5% (50.2–64.4)	22.4% (18.3–27.1)
Treatable by cryotherapy	60.9% (55.8–65.7)	42.5% (35.6–49.8)	77.6% (72.9–81.7)
Gynecologist triage			
Not treatable by cryotherapy	51.6% (46.0–57.1)	63.8% (56.1–70.7)	40.3% (33.2–47.9)
Treatable by cryotherapy	48.4% (42.9–54.0)	36.2% (29.3–43.9)	59.7% (52.1–66.8)
<i>P</i>	<0.01	0.07	<0.01

\* Based on worst histology or HPV testing in PEG clinical record review. Note: disease status was determined independent of lead reviewers' consensus evaluation.

<sup>†</sup> At study exit, women positive for the same HPV type(s) detected at enrollment or diagnosed at any time in PEG with CIN2+.

<sup>‡</sup> As determined by consensus evaluation of lead reviewers using all clinical record review and cervical images from all visits.<sup>3</sup>