Research Article

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Human Papillomavirus Genotype-Specific Prevalence across the Continuum of Cervical Neoplasia and Cancer

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Abstract

Background: The New Mexico HPV Pap Registry was established to measure the impact of cervical cancer prevention strategies in the United States. Before widespread human papillomavirus (HPV) vaccine implementation, we established the baseline prevalence for a broad spectrum of HPV genotypes across the continuum of cervical intraepithelial neoplasia (CIN) and cancer.

Methods: A population-based sample of 6,272 tissue specimens was tested for 37 HPV genotypes. The number of specimens tested within each diagnostic category was: 541 negative, 1,411 CIN grade 1 (CIN1), 2,226 CIN grade 2 (CIN2), and 2,094 CIN grade 3 (CIN3) or greater. Age-specific HPV prevalence was estimated within categories for HPV genotypes targeted by HPV vaccines.

Results: The combined prevalence of HPV genotypes included in the quadrivalent and nonavalent vaccines increased from 15.3% and 29.3% in CIN1 to 58.4% and 83.7% in CIN3, respectively. Prevalence of HPV types included in both vaccines tended to decrease with increasing age for CIN1, CIN2, CIN3, and squamous cell carcinoma (SCC), most notably for CIN3 and SCC. The six most common HPV types in descending order of prevalence were HPV-16, -31, -52, -58, -33, and -39 for CIN3 and HPV-16, -18, -31, -45, -52, and -33 for invasive cancers.

Conclusions: Health economic modeling of HPV vaccine impact should consider age-specific differences in HPV prevalence.

Impact: Population-based HPV prevalence in CIN is not well described, but is requisite for longitudinal assessment of vaccine impact and to understand the effectiveness and performance of various cervical screening strategies in vaccinated and unvaccinated women. *Cancer Epidemiol Biomarkers Prev; 24(1); 230–40. ©2014 AACR.*

Introduction

HPV16 and 18 cause approximately 70% of cervical cancer (1, 2) and 40% to 60% of cervical precancerous lesions (3, 4), and HPV6 and 11 cause >90% of genital warts (5). In 2006, the first of two human papillomavirus (HPV) vaccines, Gardasil (Merck), targeting HPV6, 11, 16, and 18 (quadrivalent vaccine) was approved by the FDA for use in females 9 to 26-years-old. The quadrivalent vaccine was subsequently approved for males ages 9 to 26 years for prevention of genital warts and for males and females ages 9 to 26 years for the prevention of anal precancers and cancers attributed to HPV6/11/16/18. In 2009, a second vaccine, Cervarix (GSK), targeting HPV16 and 18 (bivalent HPV vaccine) was approved by the FDA for use in women ages 10 to 25 years. A next-generation HPV vaccine targeting nine HPV genotypes (HPV6, 11, 16, 18, 31, 33, 45, 52, and 58) is currently under evaluation by the FDA (5).

The New Mexico HPV Pap Registry (NMHPVPR) was established in 2006 to monitor the impacts of primary and secondary cervical cancer prevention via vaccination, screening, diagnosis and treatment, and to document time trends in utilization and outcomes associated with these prevention tools. Toward assessing the true clinical benefits and costs of implementing new cervical cancer prevention technologies on the outcomes of interest, we have conducted large population-based research evaluations, including studies of approximately 60,000 residual cytology specimens and studies of archival cervical biopsy specimens from more than 6,000 women. These baselines measure HPV prevalence before widespread coverage of HPV vaccines in New Mexico. Results of the HPV genotyping of the cytology specimens have been reported (6). Here, we report the results of the tissue-based HPV genotyping of cervical biopsies with complete overlap (2007–2009) of the sampling time frame used for the cytology specimen evaluation (6). Ongoing efforts to link HPV vaccination with cervical cancer screening and outcomes will permit the measurement of the impact of HPV vaccination on the population by comparing with these baseline data and will inform the integration of HPV vaccination and screening.

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Materials and Methods

Population and sample selection

The population consists of women residing in New Mexico who had one or more cervical biopsies, including excisional biopsies, but not endocervical curettages only, during the period 2006 to 2009. We restricted the population to women with a biopsy specimen located at one of four in-state laboratories. These 21,297 women accounted for 77% of all women who had cervical biopsies in New Mexico during this time period. For women with more than one cervical biopsy during the period, we identified the biopsy with the highest grade (worst) community diagnosis and when there was more than one biopsy with this diagnosis we selected the earliest. We attempted to obtain residual blocks from all biopsies with a community diagnosis of CIN2 or more severe ($CIN2^+$) and randomly sampled 400 CIN1 biopsies and 200 negative biopsies per laboratory. Overall, we were able to locate, retrieve, and successfully test for HPV genotypes in one or more tissue blocks from 6,272 women. The population and final sample counts are given in Supplementary Table S1. Notably, the final sample included 90% of women in the population with a biopsy of $CIN2^+$. This study was approved by the University of New Mexico Human Research Review Committee.

Tissue preparation and HPV genotyping

A "sandwich" technique was used to enable histopathologic review of tissue sections flanking the sections subjected to HPV genotyping as follows: One 4-μm section was obtained for hematoxylin and eosin (H&E) staining, two 4-μm sections for HPV genotyping were collected into o-ringed microfuge tubes, a second 4-μm section was obtained for H&E staining, and, when possible, additional 4-μm sections were collected onto Fisherbrand Superfrost Plus glass slides for future biomarker evaluations.

Without removal of paraffin wax, the tissue sections obtained for HPV genotyping were resuspended (50–125 μL) in 10 mmol/L Tris pH 8.0 containing 1-mm EDTA, 0.1% Laureth-12 and 1 mg/mL proteinase K and digested with shaking at 65°C for 4 hours followed by overnight at 37°C. Before PCR-based HPV genotyping, proteinase K was inactivated at 95°C for 15 minutes. Microfuge tubes were immediately centrifuged briefly at 13,000 × *g*, whereas the paraffin-wax was liquefied and an aqueous-wax interface formed upon cooling. The aqueous digest (2 and 5 μL) from each tissue specimen was used for genotyping with the LINEAR ARRAY HPV Genotyping Test (HPV LA; Roche Diagnostics). The HPV LA Genotyping Test is a qualitative test for 37 HPV genotypes incorporating selective PCR amplification with biotinylated PGMY 09/11 L1 region consensus primers and colorimetric detection of amplified products bound to immobilized HPV genotype–specific oligonucleotide probes on a LINEAR ARRAY HPV genotyping strip. PGMY-based HPV genotyping with the HPV LA and a prototype Line Blot assay have been previously reported in detail (7–9). Using the Roche HPV LA Detection Kit, hybridizations were automated using Tecan ProfiBlot-48 robots (Tecan) as previously described (6). The Roche HPV LA Genotyping Test detects 13 high- and 24 low-risk HPV types. HPV 52 is not determined directly by a type-specific probe but rather by a probe that cross hybridizes with HPV 33, 35, 52, and 58. The presence of HPV 52 was inferred only if the cross-reactive probe was hybridized but there was no hybridization detected for the HPV 33, 35, and 58 type-specific probes. Notably, concurrent infections of type 52 with any or all of the three other types cannot be detected. HPV IS39 is a variant of HPV82, and we have classified HPV82 as positive if either probe is positive. Two independent readers interpreted the presence of HPV genotypes using a reference template provided by the manufacturer. Any discrepancies identified between the two readers were adjudicated by a third review.

Statistical analysis

We estimated the crude prevalence for each of 37 individual HPV types and for several combinations of HPV types. The prevalence for each individual HPV type was estimated as the proportion of women testing positive for the HPV type, with or without coinfection by other HPV types. For type combinations, for example, all carcinogenic HPV types combined and alpha-papillomavirus species groups (10), the prevalence was estimated as the proportion of women testing positive for one or more of the individual HPV types in the combination, with our without coinfection by HPV types not in the combination. Combinations of HPV types considered here are: (i) HPV16 or 18 combined, as targeted by the bivalent vaccine, (ii) HPV6, 11, 16, or 18 combined, as targeted by the quadrivalent vaccine, (iii) HPV6, 11, 16, 18, 31, 33, 45, 52, or 58 combined, as targeted by the nonavalent vaccine currently under review for approval by the FDA, (iv) HPV alpha-papillomavirus species groupings (alpha-3 includes hpv61, 62, 72, 81, 83, or 84; alpha-5 includes hpv26, 51, 69, or 82; alpha-6 includes hpv53, 56, or 66; alpha-7 includes hpv18, 39, 45, 59, 68, or 70; alpha-9 includes hpv16, 31, 33, 35, 52, 58, or 67; alpha-10 includes hpv6, 11, 44, 55, or 74; alpha-11 includes hpv34, 64, or 73), (v) all carcinogenic HPV genotypes combined (HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68), (vi) all noncarcinogenic HPV genotypes combined [HPV6, 11, 26, 40, 42, 53–55, 61, 62, 64, 66, 67, 69–73, 81, 82, IS39, 83, 84, or 89 (also known as CP6108)], and (7) any HPV infection (carcinogenic or noncarcinogenic). We estimated HPV prevalence separately for each category of the community pathology diagnosis, for all ages combined, and by age group, using five age groups (<21, 21–25, 26–29, 30–39, and ≥40 years) or, for rare outcomes such as cancer and adenocarcinoma *in situ* (AIS), three age groups (<30, 30–39, and ≥40 years).

This study used a stratified random sample with unequal sampling fractions using 12 sampling strata defined by the community diagnosis (negative, CIN1, and CIN2 or greater) and the four laboratories that comprised the study population. To correctly estimate HPV prevalence for the population, it is necessary to account for the varying sample fractions using appropriate weights. The sample weights are given in Supplementary Table S1. Statistical methods appropriate for stratified samples were used to compute all proportions, SEs, confidence intervals, and tests of significance. We used SAS (version 9.3) procedure SURVEYFREQ to compute proportions and confidence intervals. Confidence intervals for proportions were based on the Wilson score method. SUDAAN version 11 was used to compute the Cochran–Mantel–Haenszel test for trend.

For attribution of HPV type to lesions, we considered three approaches: (i) A maximum estimate of attribution, which was defined as the crude prevalence of the individual HPV-type or type combination and computed as described above; (ii) a minimum estimate of attribution, which was defined for individual HPV types as the proportion of all lesions with a single infection of the specific HPV type. That is, lesions with multiple HPV infections are included in the denominator but not the numerator. For type combinations, the minimum estimate is the proportion of all lesions with

Table 1. Prevalence of 37 individual HPV types, irrespective of HPV coinfections, stratified by community diagnosis

HPV type	Negative ($n = 541$) % (95% CI)	CIN1[a] ($n = 1,411$) % (95% CI)	CIN2[b] ($n = 2,226$) % (95% CI)	CIN3[c] ($n = 1,880$) % (95% CI)	AIS ($n = 51$) % (95% CI)	SCC[d] ($n = 116$) % (95% CI)	ADC ($n = 47$) % (95% CI)
6	0.2 (0.0–1.0)	3.0 (2.2–4.2)	2.1 (1.6–2.8)	1.2 (0.8–1.8)	1.9 (0.3–10.2)	0.8 (0.1–4.7)	0.0 (—)
11	0.0 (—)	1.1 (0.6–2.0)	0.5 (0.3–1.0)	0.3 (0.1–0.6)	0.0 (—)	0.0 (—)	0.0 (—)
16	4.3 (2.4–7.9)	8.2 (6.7–9.9)	34.9 (33.0–36.9)	54.1 (51.8–56.3)	43.6 (30.9–57.2)	60.2 (51.1–68.7)	21.4 (12.1–35.0)
18	1.4 (0.5–3.8)	4.4 (3.4–5.8)	5.9 (5.0–6.9)	4.9 (4.0–5.9)	48.1 (35.0–61.4)	8.6 (4.7–15.1)	17.7 (9.4–31.0)
26	0.0 (—)	0.4 (0.2–1.1)	0.5 (0.3–0.9)	0.1 (0.0–0.3)	0.0 (—)	0.9 (0.2–4.7)	0.0 (—)
31	3.8 (2.0–7.2)	4.7 (3.6–6.1)	14.4 (13.0–15.9)	14.9 (13.4–16.6)	4.1 (1.2–13.5)	5.2 (2.4–10.8)	0.0 (—)
33	0.1 (0.0–0.9)	1.9 (1.2–2.9)	4.2 (3.4–5.1)	5.2 (4.3–6.3)	3.8 (1.0–13.0)	3.4 (1.3–8.4)	0.0 (—)
35	0.5 (0.1–2.9)	2.3 (1.5–3.3)	5.9 (5.0–7.0)	4.4 (3.6–5.5)	5.7 (1.9–15.6)	0.8 (0.1–4.7)	2.0 (0.4–11.0)
39	1.0 (0.3–2.8)	7.4 (6.0–9.1)	7.7 (6.7–8.9)	4.6 (3.7–5.7)	3.8 (1.0–13.0)	2.5 (0.8–7.2)	2.0 (0.4–11.0)
40	0.0 (—)	0.9 (0.5–1.7)	0.4 (0.2–0.8)	0.6 (0.4–1.1)	0.0 (—)	0.0 (—)	0.0 (—)
42	0.7 (0.2–2.8)	1.2 (0.7–2.0)	1.6 (1.1–2.2)	1.0 (0.6–1.5)	0.0 (—)	1.0 (0.2–5.3)	0.0 (—)
45	2.0 (0.9–4.8)	2.1 (1.4–3.1)	3.0 (2.3–3.7)	2.2 (1.6–3.0)	7.9 (3.1–18.6)	4.2 (1.8–9.6)	4.1 (1.1–14.0)
51	1.3 (0.6–3.1)	7.3 (5.9–8.9)	9.1 (8.0–10.4)	4.9 (4.0–6.0)	3.8 (1.0–13.0)	1.7 (0.5–6.0)	2.0 (0.4–11.0)
52	1.6 (0.7–3.9)	4.4 (3.4–5.7)	8.3 (7.2–9.5)	7.5 (6.4–8.8)	0.0 (—)	4.2 (1.8–9.5)	0.0 (—)
53	0.9 (0.3–2.7)	5.4 (4.2–6.9)	4.1 (3.4–5.1)	2.1 (1.5–2.9)	0.0 (—)	0.8 (0.1–4.7)	0.0 (—)
54	0.2 (0.0–1.1)	1.9 (1.2–2.9)	1.0 (0.7–1.5)	1.0 (0.7–1.6)	2.3 (0.4–11.2)	0.0 (—)	0.0 (—)
55	0.0 (—)	0.6 (0.3–1.3)	0.4 (0.2–0.8)	0.4 (0.2–0.8)	0.0 (—)	0.0 (—)	0.0 (—)
56	0.5 (0.1–2.9)	5.7 (4.5–7.2)	3.8 (3.1–4.7)	1.2 (0.8–1.8)	2.3 (0.4–11.2)	0.8 (0.1–4.7)	0.0 (—)
58	2.5 (1.2–5.5)	4.1 (3.1–5.4)	8.6 (7.5–9.8)	6.3 (5.2–7.4)	1.9 (0.3–10.2)	1.7 (0.5–6.0)	4.2 (1.1–14.1)
59	1.2 (0.5–3.0)	3.2 (2.4–4.3)	4.7 (3.9–5.7)	2.5 (1.9–3.3)	1.9 (0.3–10.2)	3.4 (1.3–8.4)	0.0 (—)
61	0.0 (—)	1.0 (0.5–1.8)	0.8 (0.5–1.2)	0.7 (0.4–1.2)	0.0 (—)	0.0 (—)	0.0 (—)
62	0.8 (0.2–2.7)	0.7 (0.4–1.3)	1.1 (0.7–1.6)	0.5 (0.3–1.0)	0.0 (—)	0.8 (0.1–4.7)	0.0 (—)
64	0.0 (—)	0.1 (0.0–0.7)	0.0 (—)	0.0 (—)	0.0 (—)	0.0 (—)	0.0 (—)
66	2.0 (0.9–4.7)	6.6 (5.3–8.2)	4.8 (4.0–5.8)	2.6 (2.0–3.4)	8.3 (3.3–19.1)	1.7 (0.5–6.0)	2.1 (0.4–11.1)
67	0.1 (0.0–0.8)	1.8 (1.2–2.8)	2.4 (1.9–3.1)	1.2 (0.8–1.8)	0.0 (—)	0.0 (—)	0.0 (—)
68	0.6 (0.1–2.8)	1.5 (0.9–2.4)	1.4 (1.0–1.9)	1.0 (0.6–1.6)	0.0 (—)	2.5 (0.8–7.2)	0.0 (—)
69	0.0 (—)	0.1 (0.0–0.4)	0.2 (0.1–0.5)	0.4 (0.2–0.8)	0.0 (—)	0.0 (—)	0.0 (—)
70	0.6 (0.2–1.7)	1.4 (0.8–2.3)	1.1 (0.7–1.6)	0.5 (0.3–0.9)	0.0 (—)	0.0 (—)	0.0 (—)
71	0.0 (—)	0.0 (—)	0.0 (0.0–0.3)	0.0 (—)	0.0 (—)	0.8 (0.1–4.7)	0.0 (—)
72	0.0 (—)	0.3 (0.1–0.7)	0.0 (0.0–0.3)	0.1 (0.0–0.4)	0.0 (—)	0.0 (—)	0.0 (—)
73	0.1 (0.0–1.0)	1.3 (0.8–2.1)	2.6 (2.0–3.3)	1.9 (1.4–2.6)	0.0 (—)	1.7 (0.5–6.0)	0.0 (—)
81	0.0 (—)	0.0 (0.0–0.4)	0.4 (0.2–0.7)	0.1 (0.0–0.4)	0.0 (—)	0.0 (—)	0.0 (—)
82	0.6 (0.1–2.8)	1.5 (1.0–2.4)	2.7 (2.1–3.5)	2.1 (1.5–2.8)	0.0 (—)	0.0 (—)	0.0 (—)
82 (variant IS39)	0.0 (—)	0.3 (0.1–0.8)	0.3 (0.1–0.6)	0.2 (0.1–0.6)	0.0 (—)	0.0 (—)	0.0 (—)
83	0.0 (—)	0.1 (0.0–0.5)	0.2 (0.1–0.5)	0.4 (0.2–0.8)	0.0 (—)	0.0 (—)	0.0 (—)
84	0.5 (0.1–2.9)	1.0 (0.6–1.8)	0.9 (0.6–1.4)	0.6 (0.3–1.1)	1.9 (0.3–10.2)	0.0 (—)	0.0 (—)
89	1.3 (0.4–3.8)	1.6 (1.0–2.6)	2.0 (1.5–2.6)	1.4 (0.9–2.0)	2.3 (0.4–11.2)	2.7 (0.9–7.5)	0.0 (—)

[a]CIN1 includes 249 diagnoses of low-grade lesion without specification of CIN.
[b]CIN2 includes 188 diagnoses of CIN1/2.
[c]CIN3 includes 69 diagnoses of high-grade lesion without specification of CIN, 475 diagnoses of CIN2/3, and 222 diagnoses of CIS.
[d]SCC includes 4 diagnoses of carcinoma without specification of histologic type.

one or more of the HPV types in the combination and without coinfection with additional HPV types not in the type combination; and (iii) a proportional estimate of attribution, which was computed in the manner described by Insinga and colleagues (11). This estimate adds a fractional amount to the minimum estimate of attribution to account for lesions with multiple HPV infections. The fractional amount for each HPV type in the multitype infection is based on its relative frequency among lesions in the same diagnostic category with single HPV infections. For type combinations, the proportional estimate is the sum of the proportional estimates for all HPV types in the combination.

Results

Included in our overall analysis were biopsies with the following community diagnoses: 541 negative, 1,411 CIN1, 2,226 CIN2, and 2,094 CIN3 or more severe (CIN3$^+$), which included 1,880 CIN3, 51 AIS, 116 squamous cell carcinoma (SCC), and 47 adenocarcinoma (ADC). The median and range of age in years by diagnosis were: 31 (14–82) for negative; 25 (13–74) for CIN1; 25 (14–74) for CIN2; 28 (15–90) for CIN3; 35 (19–59) for AIS; 45 (21–88) for SCC; and 55 (27–89) for ADC.

The crude prevalence of each of the 37 individual HPV types examined in this study is shown in Table 1 and for selected HPV types, type combinations and groupings in Table 2. Negative biopsies had the lowest prevalence of any HPV of 24.9% and any carcinogenic HPV type of 19.5%. Among abnormal biopsies, the percentage of HPV16-positive increased from 8.2% in CIN1 to 54.1% in CIN3, 43.6% in AIS, and 60.2% in SCC. The percentage of HPV18 positive was <10% in all grades of CIN and SCC but increased to 48.1% in AIS. The percentage positive for types included in the quadrivalent HPV vaccine, HPV6, 11, 16, and 18, increased from 15.3% in CIN1 to 58.4% in CIN3, 87.9% in AIS, and 67.9% in SCC. Notably, HPV6, 11, 16, and 18 accounted for only 3.5% more CIN1, and less than 2% more CIN2$^+$ diagnoses than HPV16 and HPV18. The percentage of positive for nine HPV genotypes included in a next-generation HPV vaccine increased from 29.3% in CIN1 to 83.7% in CIN3, 93.9% in AIS, and 79.9% in SCC. The increase in the percent positive for these 9 HPV types versus the 4 quadrivalent HPV vaccine types was 14.0% in CIN1, 28.7% in CIN2, 25.3% in

Table 2. HPV prevalence, irrespective of HPV coinfections, stratified by community diagnosis

HPV	Negative ($n = 541$) % (95% CI)	CIN1[a] ($n = 1,411$) % (95% CI)	CIN2[b] ($n = 2,226$) % (95% CI)	CIN3[c] ($n = 1,880$) % (95% CI)	AIS ($n = 51$) % (95% CI)	SCC[d] ($n = 116$) % (95% CI)	ADC ($n = 47$) % (95% CI)
16	4.3 (2.4–7.9)	8.2 (6.7–9.9)	34.9 (33.0–36.9)	54.1 (51.8–56.3)	43.6 (30.9–57.2)	60.2 (51.1–68.7)	21.4 (12.1–35.0)
18	1.4 (0.5–3.8)	4.4 (3.4–5.8)	5.9 (5.0–6.9)	4.9 (4.0–5.9)	48.1 (35.0–61.4)	8.6 (4.7–15.1)	17.7 (9.4–31.0)
16, 18	5.7 (3.4–9.5)	11.8 (10.1–13.8)	39.6 (37.6–41.7)	58.0 (55.7–60.2)	87.9 (76.2–94.3)	67.9 (59.0–75.7)	36.7 (24.4–51.0)
6, 11, 16, 18	5.9 (3.5–9.7)	15.3 (13.3–17.5)	41.3 (39.3–43.3)	58.4 (56.2–60.7)	87.9 (76.2–94.3)	67.9 (59.0–75.7)	36.7 (24.4–51.0)
6, 11, 16, 18, 31, 33, 45, 52, 58	16.0 (11.9–21.1)	29.3 (26.8–32.0)	70.0 (68.1–71.9)	83.7 (82.0–85.3)	93.9 (83.8–97.9)	79.9 (71.7–86.2)	42.9 (29.8–57.0)
Alpha-3[e]	2.6 (1.2–5.6)	4.5 (3.5–5.9)	4.7 (3.9–5.7)	3.4 (2.7–4.3)	4.1 (1.2–13.5)	3.5 (1.4–8.6)	0.0 (—)
Alpha-5[e]	1.9 (0.9–4.2)	9.2 (7.7–11.0)	12.0 (10.7–13.4)	7.0 (5.9–8.2)	3.8 (1.0–13.0)	2.5 (0.9–7.3)	2.0 (0.4–11.0)
Alpha-6[e]	2.8 (1.4–5.7)	16.1 (14.1–18.4)	11.5 (10.2–12.9)	5.4 (4.4–6.5)	8.3 (3.3–19.1)	2.5 (0.8–7.2)	2.1 (0.4–11.1)
Alpha-7[e]	6.8 (4.4–10.4)	18.8 (16.7–21.1)	21.4 (19.8–23.2)	14.7 (13.1–16.3)	57.9 (44.3–70.4)	21.2 (14.7–29.5)	21.8 (12.4–35.5)
Alpha-9[e]	13.0 (9.3–17.9)	24.4 (22.0–26.9)	69.3 (67.3–71.1)	83.0 (81.2–84.6)	47.3 (34.3–60.7)	68.8 (59.8–76.5)	27.6 (16.9–41.7)
Alpha-10[e]	0.2 (0.0–1.0)	4.7 (3.6–6.1)	3.1 (2.5–3.9)	1.7 (1.2–2.4)	1.9 (0.3–10.2)	0.8 (0.1–4.7)	0.0 (—)
Alpha-11[e]	0.1 (0.0–1.0)	1.4 (0.9–2.3)	2.6 (2.0–3.3)	1.9 (1.4–2.6)	0.0 (—)	1.7 (0.5–6.0)	0.0 (—)
Any carcinogenic[f]	19.5 (15.0–24.8)	45.7 (43.0–48.4)	85.3 (83.7–86.7)	91.3 (90.0–92.5)	93.9 (83.8–97.9)	87.4 (80.1–92.3)	44.9 (31.6–59.0)
Any noncarcinogenic[g]	7.2 (4.6–10.9)	25.6 (23.2–28.1)	24.4 (22.6–26.2)	15.4 (13.8–17.1)	12.1 (5.7–23.7)	10.4 (6.1–17.3)	2.1 (0.4–11.1)
Any HPV[h]	24.9 (20.0–30.5)	60.8 (58.2–63.3)	92.6 (91.4–93.6)	95.2 (94.2–96.1)	93.9 (83.8–97.9)	90.1 (83.3–94.4)	44.9 (31.6–59.0)
Single-type infection[i]	21.5 (16.9–27.0)	41.7 (39.0–44.5)	59.9 (57.9–62.0)	68.9 (66.8–71.0)	66.4 (52.7–77.8)	74.9 (66.3–81.9)	34.2 (22.3–48.5)
Multiple-type infection[j]	3.4 (1.8–6.2)	19.1 (17.0–21.5)	32.7 (30.7–34.6)	26.3 (24.4–28.3)	27.5 (17.2–41.0)	15.2 (9.8–22.9)	10.7 (4.7–22.7)

[a]CIN1 includes 249 diagnoses of low-grade lesion without specification of CIN.
[b]CIN2 includes 188 diagnoses of CIN1/2.
[c]CIN3 includes 69 diagnoses of high-grade lesion without specification of CIN, 475 diagnoses of CIN2/3, and 222 diagnoses of CIS.
[d]SCC includes 4 diagnoses of carcinoma without specification of histologic type.
[e]HPV alpha species: alpha-3 is hpv61, 62, 72, 81, 83, or 84; alpha-5 is hpv26, 51, 69, or 82; alpha-6 is hpv53, 56, or 66; alpha-7 is hpv18, 39, 45, 59, 68, or 70; alpha-9 is hpv16, 31, 33, 35, 52, 58, or 67; alpha-10 is hpv6, 11, 44, 55, or 74; alpha-11 is hpv34, 64, or 73.
[f]Any carcinogenic HPV is detection of one or more of HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68.
[g]Any noncarcinogenic HPV is detection of one or more of HPV6, 11, 26, 40, 42, 53–55, 61, 62, 64, 66, 67, 69–73, 81, 82, IS39, 83, 84, or 89 (also known as CP6108).
[h]Any HPV is detection of one or more of the 37 HPV types listed individually in Table 1.
[i]Single-type infection is detection of only one of the 37 HPV types.
[j]Multiple-type infection is detection of more than one of the 37 HPV types.

CIN3, and 12.0% in SCC. Fewer than half (44.9%) of ADC were positive for any type of HPV, although all of these were positive for at least one carcinogenic HPV type and only 2.1% were positive for any noncarcinogenic HPV type.

Table 2 also shows the prevalence of alpha papillomavirus species groups -3, -5, -6, -7, -9, -10, -11 and single and multiple HPV infections by community pathology diagnosis. Alpha-7 and -9 species were detected in 14.7% and 83% of CIN3, respectively, but in 57.9% and 47.3% of AIS. More than one HPV type was detected in 3.4% of negative biopsies, 19.1% of CIN1, 32.7% CIN2, 26.3% of CIN3, 27.5% of AIS, 15.2% of SCC, and 10.7% of ADC lesions. The ratio of single to multiple infections was greatest for negative biopsies (6.1) and ranged from 1.8 to 2.6 in biopsies of grade CIN1 to CIN3, or AIS. In cancers, the ratio of single to multiple infections increased to 4.9 for SCC and 3.2 for ADC.

Stratification of HPV prevalence by age for the types targeted by the bivalent, quadrivalent, and nonavalent vaccines as well as for other groupings of HPV types included in our evaluation is shown in Fig. 1 and Tables 3 and 4. Although the sample size was smaller for older women, the prevalence of alpha-9 papillomavirus species in AIS was 74.4%, 44.4%, and 17.4% in women ages <30 years, 30 to 39 years, and ≥40 years, respectively. In contrast, the alpha-7 papillomavirus species increased in AIS across these same age groups (49.5%, 64.2%, and 64.2%, respectively). The relative percentage of HPV positive by diagnosis within age groups followed similar patterns to the percentage of HPV positive for all age groups combined. With the exception of the <21 year age group, which according to newly updated guidelines should not be screened at all (12, 13), the absolute percentage of HPV positive in CIN1, CIN2, CIN3, and SCC for HPV types included in the bivalent, quadrivalent, and nonavalent HPV vaccines tended to decrease with increasing age, although the age-related decrement for CIN2 or any HPV was less for the nonavalent vaccine ($P = 0.0212$ and $P = 0.1308$, respectively).

We also estimated HPV prevalence for specimens in which a single HPV type was detected. As shown in Table 5, the frequency for HPV6, 11, 16, and 18 combined was 17.5%, 40.4%, 58.2%, 73.7%, and 90.9% in specimens diagnosed as CIN1, CIN2, CIN3, SCC, and AIS, respectively. The frequency of HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 combined was 39.8%, 71.3%, 86.1%, 87.4%, and 100% in specimens diagnosed as CIN1, CIN2, CIN3, SCC, and AIS, respectively. For CIN2 and CIN3, estimates of HPV frequencies in specimens in which only a single HPV type was detected were similar to estimates for all specimens irrespective of HPV coinfections. Supplementary Table S2 provides these estimates for all 37 individual HPV types.

In Table 6, we present three estimates of the proportion of lesions within a diagnostic category that are attributable to specific HPV types and combinations of types: (i) a minimum estimate, which ignores any contribution from multitype infections, (ii) a maximum estimate, which assumes that all lesions positive for the HPV type, regardless of coinfection with other types, are attributable to that type, and (iii) a proportional estimate, intermediate to the minimum and maximum estimates, which apportions the contribution of HPV types in multitype infections according to their relative frequency among single-type infections. The proportional estimate of attribution is close to the maximum estimate for the high-prevalence carcinogenic HPV types 16 and 31, and for combinations that contain these types. For the lower-prevalence carcinogenic types, the proportional estimate is intermediate to the minimum and maximum estimates of attribution, and for noncarcinogenic HPV types the proportional estimate is close to the minimum.

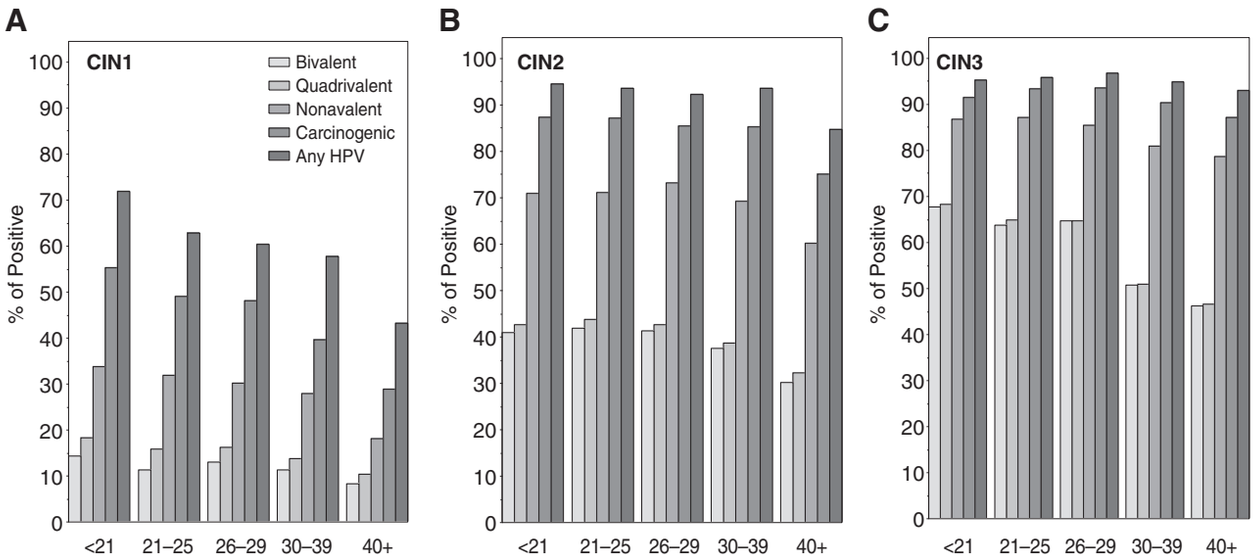

Figure 1.
Age-group trends in the HPV-type attribution for HPV16 and HPV18 (bivalent), HPV6, 11, 16, and 18 (quadrivalent), and HPV6, 11, 16, 18, 31, 33, 45, 52, and 58 (nonavalent) in CIN1 (A), CIN2 (B), and CIN3 (C). Tests for age trend are shown below. CIN1: bivalent, $P = 0.1086$; quadrivalent, $P = 0.0232$; nonavalent, $P = 0.0003$; carcinogenic, $P < 0.0001$; any HPV, $P < 0.0001$; CIN2: bivalent, $P = 0.0053$; quadrivalent, $P = 0.0047$; nonavalent, $P = 0.0212$; carcinogenic, $P = 0.0005$; any HPV, $P = 0.0015$; and CIN3: bivalent, $P < 0.0001$; quadrivalent, $P < 0.0001$; nonavalent, $P = 0.0003$; carcinogenic, $P = 0.0091$; any HPV, $P = 0.1308$.

Discussion

Because of the nature of a population-based study (vs. a case study), as well as the rarity of cancers in the United States and the long interval between infection and cancer, the most common endpoints are the clinically actionable precancerous lesions, CIN2, CIN3, and AIS, which trigger excisional treatments. CIN3 in older women has a 30% risk of becoming invasive cancer over 30 years (14). With widespread coverage of current HPV vaccines, on the basis of our data we suggest that in the U.S. population approximately 40% of CIN2, 58% of CIN3, and 90% of AIS could be averted. Similarly, on the basis of these data, the nonavalent vaccine, if and when it becomes available, might be expected to prevent 70% of CIN2, 84% of CIN3, and 94% of AIS.

Microdissection was not used in this study. Thus, as in any study using whole-tissue sections, detection of multiple HPV types in biopsy specimens is common. Though hierarchical and proportional approaches have been applied to estimate causal attribution (15, 16) when multiple HPV infections are detected in single biopsy specimens, these methods are not without problems and produce estimates that remain uncertain. For our main analyses, we therefore chose to consider all lesions irrespective of HPV coinfections as a maximum attribution approach. We compared these frequencies using the subset of biopsy specimens in which a single HPV type was detected. For CIN2 and CIN3, estimates of HPV frequencies among lesions with a single HPV-type detected were very similar to estimates for all lesions irrespective of HPV coinfections.

We also considered a proportional approach to estimate disease attribution. The proportional and maximum attribution methods converged for HPV16/18 as the grade of abnormality increased. Irrespective of the attribution method or grade of CIN, the most frequent type detected was HPV16.

HPV vaccination against HPV16 and 18 is expected to have the greatest impact on cervical precancer and cancer diagnoses compared with all other HPV types combined (17, 18). HPV16-related CIN3 or CIN2/3 occurs at a younger age (19–21), consistent with HPV16- and HPV18-related cervical cancers occurring at younger age (2, 3) compared with cervical cancers caused by other HPV types. Another observation from these data relevant to assessing HPV vaccine impact is the fractional contribution of other carcinogenic HPV genotypes to the proportion of high-grade CIN that will be removed from the population by vaccination. Or conversely, that fraction that potentially needs closer monitoring or treatment in the absence of vaccination. In this regard, the contribution of HPV31 in CIN2$^+$ stands out in the data, perhaps because of its close phylogenetic and therefore biologic relationship to HPV16. This is followed by a cluster of HPV types of almost similar import namely HPV33, 35, 52, and 58. Only HPV 35 is not targeted by the nonavalent vaccine.

Our data show that the percentage positive for HPV types included in the bivalent, quadrivalent, and nonavalent HPV vaccines in CIN1, CIN2, CIN3, and SCC tended to decrease with increasing age. This was somewhat surprising as, theoretically, CIN of any grade is almost entirely attributable to HPV. As can be seen in both Fig. 1 and Table 3, the age-related decrement in HPV prevalence is greater for biopsies interpreted as CIN1 than for CIN2 or CIN3$^+$. These patterns hold true for almost all HPV types and combinations with the exception of HPV18. HPV18 is associated with lesions in the endocervical canal that may be more difficult to detect and in cohorts with long-term follow-up, such as Kaiser Portland Oregon, the detection of HPV-associated CIN3 lags by several years for HPV18 (22, 23). In addition, it is possible that at least some of the age-related decrease with increasing age may well be due to age-related misclassification of lesion histopathology or morphologies that are HPV negative, and therefore not truly CIN. It should be noted that the age-related decrement in

Table 3. HPV prevalence, irrespective of HPV coinfections, stratified by age for biopsies with community diagnosis of negative and CIN1–CIN3

Diagnosis	HPV	<21 y % (95% CI)	21–25 y % (95% CI)	26–29 y % (95% CI)	30–39 y % (95% CI)	40+ y % (95% CI)
Negative ($n = 541$)	16	1.2 (0.2–6.9)	5.2 (1.7–15.0)	5.4 (1.4–19.0)	5.5 (1.6–16.8)	4.2 (1.3–12.8)
	18	0.3 (0.0–5.4)	2.6 (0.6–11.2)	4.6 (1.0–19.1)	0.3 (0.0–4.0)	0.3 (0.0–2.7)
	16, 18	1.5 (0.3–7.4)	7.9 (3.1–18.4)	10.0 (3.5–25.5)	5.8 (1.8–16.9)	4.5 (1.5–12.9)
	6, 11, 16, 18	2.0 (0.5–8.2)	8.2 (3.4–18.6)	10.0 (3.5–25.5)	5.8 (1.8–16.9)	4.5 (1.5–12.9)
	6, 11, 16, 18, 31, 33, 45, 52, 58	13.6 (6.4–26.6)	17.8 (10.0–29.6)	24.3 (12.6–41.7)	19.4 (10.8–32.5)	9.4 (4.4–18.9)
	Alpha-7[d]	5.7 (2.0–15.5)	7.3 (3.1–16.2)	11.1 (4.2–26.1)	10.3 (4.9–20.1)	2.5 (0.6–9.6)
	Alpha-9[d]	13.3 (6.2–26.3)	16.7 (9.1–28.6)	20.2 (9.8–37.1)	12.0 (5.4–24.5)	7.1 (3.0–16.1)
	Alpha-10[d]	0.5 (0.0–5.7)	0.4 (0.0–4.0)	0.0 (—)	0.0 (—)	0.0 (—)
	Carcinogenic[e]	15.0 (7.5–27.7)	29.2 (19.1–42.0)	25.7 (13.8–42.8)	21.3 (12.4–34.3)	9.7 (4.6–19.2)
	Noncarcinogenic[f]	15.3 (7.3–29.4)	10.9 (5.4–20.7)	8.9 (3.5–20.9)	1.6 (0.4–6.2)	2.2 (0.5–9.7)
	Any HPV[g]	29.4 (17.9–44.4)	33.4 (22.7–46.2)	34.1 (20.5–50.8)	23.0 (13.8–35.7)	11.9 (6.1–21.9)
CIN1[a] ($n = 1,411$)	16	9.5 (6.5–13.7)	8.3 (5.9–11.6)	10.3 (6.6–15.8)	6.4 (3.8–10.5)	5.6 (2.9–10.4)
	18	5.2 (3.0–8.8)	3.7 (2.1–6.2)	4.1 (2.2–7.7)	4.9 (2.6–8.9)	4.6 (2.3–9.1)
	16, 18	14.2 (10.5–19.0)	11.2 (8.4–14.9)	13.1 (9.0–18.8)	11.3 (7.6–16.4)	8.3 (4.9–13.7)
	6, 11, 16, 18	18.4 (14.1–23.6)	15.8 (12.4–19.9)	16.1 (11.5–22.2)	13.7 (9.6–19.2)	10.4 (6.5–16.2)
	6, 11, 16, 18, 31, 33, 45, 52, 58	33.8 (28.4–39.6)	31.8 (27.2–36.9)	30.2 (24.0–37.3)	27.9 (22.2–34.4)	18.1 (13.1–24.4)
	Alpha-7[d]	23.6 (18.9–28.9)	21.2 (17.3–25.8)	19.9 (14.6–26.5)	13.9 (9.9–19.3)	10.9 (7.2–16.2)
	Alpha-9[d]	28.8 (23.8–34.5)	26.6 (22.2–31.5)	25.1 (19.3–31.9)	22.7 (17.5–28.8)	14.1 (9.7–19.9)
	Alpha-10[d]	6.1 (3.7–9.9)	5.8 (3.8–8.8)	3.3 (1.5–7.1)	3.8 (1.8–7.8)	2.4 (0.9–6.2)
	Carcinogenic	55.2 (49.4–60.8)	48.9 (43.8–54.1)	48.1 (40.9–55.3)	39.7 (33.3–46.4)	28.7 (22.7–35.6)
	Noncarcinogenic	33.0 (27.7–38.7)	24.8 (20.5–29.7)	22.4 (16.8–29.3)	25.9 (20.4–32.3)	18.1 (13.3–24.3)
	Any HPV	71.8 (66.6–76.5)	62.9 (57.9–67.6)	60.2 (53.1–67.0)	57.7 (51.1–64.0)	43.3 (36.5–50.3)
CIN2[b] ($n = 2,226$)	16	37.7 (33.3–42.2)	37.4 (34.0–40.8)	36.1 (31.4–41.1)	32.2 (27.8–36.8)	24.2 (19.1–30.3)
	18	5.1 (3.4–7.6)	5.2 (3.8–7.0)	7.5 (5.2–10.6)	6.2 (4.3–9.0)	6.4 (3.8–10.4)
	16, 18	41.0 (36.6–45.6)	41.9 (38.5–45.4)	41.4 (36.5–46.4)	37.5 (32.9–42.2)	30.1 (24.5–36.5)
	6, 11, 16, 18	42.8 (38.3–47.4)	43.8 (40.3–47.3)	42.7 (37.8–47.8)	38.6 (34.1–43.4)	32.3 (26.5–38.7)
	6, 11, 16, 18, 31, 33, 45, 52, 58	70.9 (66.5–74.9)	71.2 (67.9–74.3)	73.3 (68.6–77.6)	69.1 (64.5–73.4)	60.1 (53.5–66.3)
	Alpha-7[d]	22.3 (18.7–26.3)	22.3 (19.5–25.4)	20.5 (16.7–24.9)	20.8 (17.1–24.9)	19.8 (15.1–25.5)
	Alpha-9[d]	72.0 (67.7–75.9)	71.4 (68.1–74.5)	71.9 (67.2–76.2)	67.7 (63.0–72.0)	55.1 (48.5–61.4)
	Alpha-10[d]	4.4 (2.9–6.8)	3.3 (2.3–4.9)	2.4 (1.2–4.5)	1.9 (1.0–3.7)	3.1 (1.5–6.2)
	Carcinogenic	87.4 (84.0–90.1)	87.1 (84.5–89.3)	85.3 (81.4–88.6)	85.3 (81.6–88.4)	74.9 (68.8–80.1)
	Noncarcinogenic	32.6 (28.4–37.1)	24.6 (21.7–27.8)	20.4 (16.6–24.8)	19.4 (15.9–23.5)	22.6 (17.6–28.6)
	Any HPV	94.4 (91.9–96.2)	93.5 (91.6–95.1)	92.2 (89.0–94.5)	93.5 (90.7–95.5)	84.7 (79.4–88.8)
CIN3[c] ($n = 1,880$)	16	65.6 (58.6–72.0)	61.5 (57.2–65.6)	61.0 (55.9–65.9)	45.3 (41.1–49.7)	41.1 (35.8–46.7)
	18	4.8 (2.5–8.8)	3.5 (2.2–5.5)	4.2 (2.6–6.8)	6.5 (4.6–8.9)	5.2 (3.2–8.2)
	16, 18	67.8 (60.8–74.0)	63.8 (59.5–67.9)	64.7 (59.6–69.4)	50.8 (46.5–55.1)	46.3 (40.8–51.9)
	6, 11, 16, 18	68.3 (61.4–74.5)	65.0 (60.8–69.0)	64.7 (59.6–69.4)	51.0 (46.6–55.3)	46.6 (41.2–52.2)
	6, 11, 16, 18, 31, 33, 45, 52, 58	86.8 (81.2–90.9)	87.1 (83.9–89.7)	85.4 (81.4–88.7)	81.0 (77.4–84.2)	78.7 (73.8–82.9)
	Alpha-7[d]	15.0 (10.6–20.8)	14.5 (11.7–17.8)	14.2 (11.0–18.2)	14.8 (12.0–18.2)	15.0 (11.4–19.4)
	Alpha-9[d]	88.3 (82.9–92.1)	86.1 (82.8–88.9)	86.2 (82.3–89.4)	81.4 (77.8–84.6)	73.4 (68.2–78.0)
	Alpha-10[d]	2.7 (1.2–6.1)	2.1 (1.2–3.8)	1.3 (0.6–3.1)	1.6 (0.8–3.1)	1.0 (0.3–2.8)
	Carcinogenic	91.5 (86.6–94.7)	93.3 (90.8–95.2)	93.4 (90.4–95.5)	90.3 (87.4–92.6)	87.1 (82.9–90.4)
	Noncarcinogenic	27.2 (21.4–34.0)	16.3 (13.4–19.8)	12.1 (9.2–15.9)	13.2 (10.5–16.4)	14.0 (10.6–18.3)
	Any HPV	95.2 (91.1–97.4)	95.9 (93.8–97.3)	96.7 (94.4–98.1)	94.9 (92.7–96.5)	92.9 (89.5–95.3)

[a]CIN1 includes 249 diagnoses of low-grade lesion without specification of CIN.
[b]CIN2 includes 188 diagnoses of CIN1/2.
[c]CIN3 includes 69 diagnoses of high-grade lesion without specification of CIN, 475 diagnoses of CIN2/3, and 222 diagnoses of CIS.
[d]HPV alpha species are: alpha-7 is hpv18, 39, 45, 59, 68, or 70; alpha-9 is hpv16, 31, 33, 35, 52, 58, or 67; alpha-10 is hpv6, 11, 44, 55, or 74.
[e]Any carcinogenic HPV is detection of one or more of HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68.
[f]Any noncarcinogenic HPV is detection of one or more of HPV6, 11, 26, 40, 42, 53–55, 61, 62, 64, 66, 67, 69–73, 81, 82, IS39, 83, 84, or 89 (also known as CP6108).
[g]Any HPV is detection of one or more of the 37 HPV types listed individually in Table 1.

prevalence of HPV types prevented by the bivalent and quadrivalent vaccine was greater in some instances than that observed for the nonavalent vaccine, suggesting that benefits of the nonavalent vaccine could be greater across a broader age range.

A potential limitation of the study is that both low-grade and high-grade lesions show significant interobserver interpretive variations and these variations increase in biopsies with increasing patient age (24–26). Thus, a future analysis will more closely examine these variables by comparing independent expert adjudicated reviews of all the biopsies compared with the community pathology interpretations and correlated with the HPV genotyping data. However, on the basis of these and other data, health economic modeling of HPV vaccine impact should incorporate age-specific differences in HPV-type attribution.

We observed an increase with age in the percentage of SCC testing positive for noncarcinogenic HPV genotypes from 6.6% in women ages 30 to 39 years to 12.4% in women 40 years and older. The category of noncarcinogenic HPV includes HPV genotypes that are considered borderline carcinogenic, but rarely cause cervical cancer and are not detected in sufficient proportions to be targeted by HPV vaccines or HPV diagnostic tests. These HPV types that are detected by the LINEAR ARRAY HPV Genotyping test include HPV26, 53, 66, 67, 69, 73, and 82 (9, 10). Perhaps not surprising, these HPV types, when they do cause cancer, take

Table 4. HPV prevalence, irrespective of HPV coinfections, stratified by age for biopsies with community diagnosis of AIS, SCC, and ADC

Diagnosis	HPV	<30 y % (95% CI)	30–39 y % (95% CI)	40+ y % (95% CI)
AIS ($n = 51$)	16	69.6 (47.7–85.2)	37.5 (17.6–62.8)	17.4 (6.0–40.7)
	18	39.9 (21.8–61.3)	55.6 (31.3–77.5)	51.7 (29.9–72.8)
	16, 18	100 (—)	93.1 (68.8–98.8)	69.0 (45.3–85.7)
	6, 11, 16, 18	100 (—)	93.1 (68.8–98.8)	69.0 (45.3–85.7)
	6, 11, 16, 18, 31, 33, 45, 52, 58	100 (—)	100 (—)	81.5 (58.1–93.4)
	Alpha-7[b]	49.5 (29.5–69.6)	62.5 (37.2–82.4)	64.2 (40.8–82.3)
	Alpha-9[b]	74.4 (52.5–88.4)	44.4 (22.5–68.7)	17.4 (6.0–40.7)
	Alpha-10[b]	4.8 (0.8–23.3)	0.0 (—)	0.0 (—)
	Carcinogenic[c]	100 (—)	100 (—)	81.5 (58.1–93.4)
	Noncarcinogenic[d]	25.6 (11.6–47.5)	0.0 (—)	5.7 (1.0–26.8)
	Any HPV[e]	100 (—)	100 (—)	81.5 (58.1–93.4)
SCC[a] ($n = 116$)	16	84.8 (58.0–95.8)	70.4 (52.5–83.6)	51.8 (40.6–62.9)
	18	7.6 (1.3–33.2)	10.0 (3.4–25.6)	8.2 (3.8–16.7)
	16, 18	84.8 (58.0–95.8)	80.3 (63.0–90.7)	60.0 (48.6–70.5)
	6, 11, 16, 18	84.8 (58.0–95.8)	80.3 (63.0–90.7)	60.0 (48.6–70.5)
	6, 11, 16, 18, 31, 33, 45, 52, 58	100 (—)	83.6 (66.7–92.8)	74.9 (63.9–83.4)
	Alpha-7[b]	15.2 (4.2–42.0)	29.6 (16.4–47.5)	18.8 (11.5–29.3)
	Alpha-9[b]	100 (—)	70.4 (52.5–83.6)	62.7 (51.2–72.9)
	Alpha-10[b]	0.0 (—)	3.3 (0.6–16.6)	0.0 (—)
	Carcinogenic	100 (—)	93.4 (78.8–98.2)	82.8 (72.6–89.8)
	Noncarcinogenic	7.6 (1.3–33.2)	6.6 (1.8–21.2)	12.4 (6.7–21.9)
	Any HPV	100 (—)	93.4 (78.8–98.2)	87.1 (77.5–93.0)
ADC ($n = 47$)	16	67.1 (21.0–94.0)	36.5 (7.2–81.0)	17.0 (8.4–31.1)
	18	32.9 (6.0–79.0)	100 (—)	10.4 (4.2–23.3)
	16, 18	100 (—)	100 (—)	27.3 (16.1–42.5)
	6, 11, 16, 18	100 (—)	100 (—)	27.3 (16.1–42.5)
	6, 11, 16, 18, 31, 33, 45, 52, 58	100 (—)	100 (—)	34.4 (21.8–49.7)
	Alpha-7[b]	32.9 (6.0–79.0)	100 (—)	15.1 (7.2–28.9)
	Alpha-9[b]	67.1 (21.0–94.0)	36.5 (7.2–81.0)	24.1 (13.6–39.0)
	Alpha-10[b]	0.0 (—)	0.0 (—)	0.0 (—)
	Carcinogenic	100 (—)	100 (—)	36.8 (23.8–52.1)
	Noncarcinogenic	0.0 (—)	0.0 (—)	2.4 (0.4–12.6)
	Any HPV	100 (—)	100 (—)	36.8 (23.8–52.1)

[a]SCC includes 4 diagnoses of carcinoma without specification of histologic type.
[b]HPV alpha species are: alpha-7 is hpv18, 39, 45, 59, 68, or 70; alpha-9 is hpv16, 31, 33, 35, 52, 58, or 67; alpha-10 is hpv6, 11, 44, 55, or 74.
[c]Any carcinogenic HPV is detection of one or more of HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68.
[d]Any noncarcinogenic HPV is detection of one or more of HPV6, 11, 26, 40, 42, 53–55, 61, 62, 64, 66, 67, 69–73, 81, 82, IS39, 83, 84, or 89 (also known as CP6108).
[e]Any HPV is detection of one or more of the 37 HPV types listed individually in Table 1.

Table 5. HPV prevalence in cervical biopsies that are positive for a single HPV type, stratified by community diagnosis

HPV type	Negative ($n = 96$) % (95% CI)	CIN1[a] ($n = 583$) % (95% CI)	CIN2[b] ($n = 1,334$) % (95% CI)	CIN3[c] ($n = 1,295$) % (95% CI)	AIS ($n = 34$) % (95% CI)	SCC[d] ($n = 87$) % (95% CI)	ADC ($n = 16$) % (95% CI)
16	19.1 (10.5–32.3)	8.4 (6.3–11.2)	35.4 (32.9–38.0)	54.4 (51.7–57.1)	38.4 (24.0–55.1)	64.5 (54.1–73.8)	49.3 (27.5–71.5)
18	5.8 (1.9–16.0)	4.6 (3.0–6.8)	3.9 (3.0–5.1)	3.6 (2.7–4.8)	52.5 (36.4–68.2)	9.2 (4.7–17.1)	38.7 (19.4–62.5)
16, 18	24.9 (15.0–38.5)	13.0 (10.3–16.3)	39.3 (36.7–42.0)	58.0 (55.3–60.7)	90.9 (76.7–96.8)	73.7 (63.6–81.8)	88.1 (64.6–96.8)
6, 11, 16, 18	24.9 (15.0–38.5)	17.5 (14.4–21.1)	40.4 (37.8–43.1)	58.2 (55.5–60.8)	90.9 (76.7–96.8)	73.7 (63.6–81.8)	88.1 (64.6–96.8)
6, 11, 16, 18, 31, 33, 45, 52, 58	64.5 (51.5–75.6)	39.8 (35.6–44.1)	71.3 (68.9–73.7)	86.1 (84.1–87.9)	100 (—)	87.4 (78.9–92.9)	94.0 (72.0–99.0)
Alpha-3[e]	8.5 (3.4–19.7)	3.3 (2.0–5.2)	0.3 (0.1–0.8)	0.2 (0.1–0.7)	0.0 (—)	0.0 (—)	0.0 (—)
Alpha-5[e]	8.1 (3.5–17.6)	12.0 (9.4–15.1)	8.5 (7.1–10.1)	3.6 (2.8–4.8)	0.0 (—)	2.3 (0.6–8.0)	0.0 (—)
Alpha-6[e]	6.1 (2.1–16.1)	20.6 (17.2–24.5)	4.8 (3.8–6.1)	1.8 (1.2–2.7)	0.0 (—)	0.0 (—)	0.0 (—)
Alpha-7[e]	23.4 (14.4–35.6)	24.5 (21.0–28.5)	13.0 (11.3–14.9)	8.2 (6.8–9.8)	61.6 (44.9–76.0)	21.6 (14.2–31.3)	44.7 (23.8–67.6)
Alpha-9[e]	50.1 (37.1–63.0)	31.4 (27.5–35.5)	70.7 (68.2–73.0)	85.3 (83.2–87.1)	38.4 (24.0–55.1)	73.7 (63.6–81.8)	55.3 (32.4–76.2)
Alpha-10[e]	0.0 (—)	5.1 (3.4–7.5)	1.1 (0.7–1.8)	0.2 (0.1–0.7)	0.0 (—)	0.0 (—)	0.0 (—)
Alpha-11[e]	0.3 (0.0–4.3)	1.3 (0.6–2.6)	1.0 (0.6–1.7)	0.3 (0.1–0.8)	0.0 (—)	1.1 (0.2–6.2)	0.0 (—)
Any carcinogenic[f]	75.5 (62.8–85.0)	69.4 (65.2–73.4)	89.4 (87.7–91.0)	95.1 (93.8–96.2)	100 (—)	96.4 (90.1–98.7)	100 (—)
Any noncarcinogenic[g]	24.5 (15.0–37.2)	30.0 (26.1–34.2)	10.4 (8.8–12.1)	4.8 (3.7–6.1)	0.0 (—)	3.6 (1.3–9.9)	0.0 (—)

[a]CIN1 includes 58 diagnoses of low-grade lesion without specification of CIN.
[b]CIN2 includes 101 diagnoses of CIN1/2.
[c]CIN3 includes 47 diagnoses of high-grade lesion without specification of CIN, 306 diagnoses of CIN2/3, and 160 diagnoses of CIS.
[d]SCC includes 3 diagnoses of carcinoma without specification of histologic type.
[e]HPV alpha species: alpha-3 is hpv61, 62, 72, 81, 83, or 84; alpha-5 is hpv26, 51, 69, or 82; alpha-6 is hpv53, 56, or 66; alpha-7 is hpv18, 39, 45, 59, 68, or 70; alpha-9 is hpv16, 31, 33, 35, 52, 58, or 67; alpha-10 is hpv6, 11, 44, 55, or 74; alpha-11 is hpv34, 64, or 73.
[f]Any carcinogenic HPV is detection of one of HPV16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, or 68.
[g]Any noncarcinogenic HPV is detection of one of HPV6, 11, 26, 40, 42, 53–55, 61, 62, 64, 66, 67, 69–73, 81, 82, IS39, 83, 84, or 89 (also known as CP6108).

Table 6. Minimum, maximum, and proportional estimates of attribution of HPV type to lesion

	CIN1[a] ($n = 1,411$)			CIN2[b] ($n = 2,226$)			CIN3[c] ($n = 1,880$)			AIS ($n = 51$)			SCC[d] ($n = 116$)			ADC ($n = 47$)		
HPV type	**Min[e]**	**Prop[f]**	**Max[g]**	**Min**	**Prop**	**Max**	**Min**	**Prop**	**Max**	**Min**	**Prop**	**Max**	**Min**	**Prop**	**Max**	**Min**	**Prop**	**Max**
6	1.5	2.1	3.0	0.4	0.6	2.1	0.1	0.2	1.2	0.0	0.0	1.9	0.0	0.0	0.8	0.0	0.0	0.0
11	0.4	0.5	1.1	0.2	0.2	0.5	0.0	0.0	0.3	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
16	3.5	6.2	8.2	21.2	33.2	34.9	37.5	52.9	54.1	25.5	41.4	43.6	48.3	59.9	60.2	16.9	20.3	21.4
18	1.9	3.1	4.4	2.4	3.5	5.9	2.5	3.2	4.9	34.9	46.2	48.1	6.9	7.8	8.6	13.3	16.1	17.7
26	0.1	0.1	0.4	0.2	0.3	0.5	0.0	0.0	0.1	0.0	0.0	0.0	0.9	0.9	0.9	0.0	0.0	0.0
31	2.7	3.8	4.7	7.6	12.1	14.4	8.7	12.2	14.9	0.0	0.0	4.1	3.5	3.6	5.2	0.0	0.0	0.0
33	0.8	1.2	1.9	2.1	2.9	4.2	2.9	3.6	5.2	0.0	0.0	3.8	2.5	2.6	3.4	0.0	0.0	0.0
35	0.6	0.9	2.3	3.0	4.2	5.9	2.5	3.1	4.4	0.0	0.0	5.7	0.0	0.0	0.8	2.0	2.0	2.0
39	4.4	6.4	7.4	2.6	4.3	7.7	1.4	1.9	4.6	0.0	0.0	3.8	0.8	1.3	2.5	0.0	1.0	2.0
40	0.1	0.2	0.9	0.1	0.2	0.4	0.0	0.0	0.6	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
42	0.3	0.4	1.2	0.1	0.2	1.6	0.0	0.0	1.0	0.0	0.0	0.0	1.0	1.0	1.0	0.0	0.0	0.0
45	1.1	1.3	2.1	1.2	1.6	3.0	1.1	1.3	2.2	6.0	6.3	7.9	3.4	3.5	4.2	2.0	2.3	4.1
51	4.1	5.9	7.3	3.7	6.4	9.1	1.6	2.6	4.9	0.0	0.0	3.8	0.8	1.7	1.7	0.0	0.0	2.0
52	2.3	3.2	4.4	3.2	5.0	8.3	3.2	4.4	7.5	0.0	0.0	0.0	0.0	0.0	4.2	0.0	0.0	0.0
53	2.4	3.8	5.4	0.7	1.2	4.1	0.5	0.7	2.1	0.0	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0
54	0.4	0.6	1.9	0.1	0.2	1.0	0.2	0.3	1.0	0.0	0.0	2.3	0.0	0.0	0.0	0.0	0.0	0.0
55	0.2	0.3	0.6	0.0	0.0	0.4	0.1	0.1	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
56	3.0	4.4	5.7	1.1	1.8	3.8	0.2	0.2	1.2	0.0	0.0	2.3	0.0	0.0	0.8	0.0	0.0	0.0
58	2.4	3.2	4.1	4.4	6.6	8.6	3.4	4.4	6.3	0.0	0.0	1.9	0.8	1.3	1.7	0.0	2.1	4.2
59	1.4	1.9	3.2	0.9	1.4	4.7	0.5	0.7	2.5	0.0	0.0	1.9	2.5	2.6	3.4	0.0	0.0	0.0
61	0.3	0.4	1.0	0.0	0.0	0.8	0.0	0.0	0.7	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
62	0.2	0.3	0.7	0.1	0.1	1.1	0.1	0.1	0.5	0.0	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0
64	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
66	3.2	5.0	6.6	1.1	1.9	4.8	0.6	0.7	2.6	0.0	0.0	8.3	0.0	0.0	1.7	0.0	1.1	2.1
67	0.7	1.0	1.8	0.9	1.2	2.4	0.6	0.8	1.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
68	0.7	0.9	1.5	0.3	0.4	1.4	0.2	0.2	1.0	0.0	0.0	0.0	2.5	2.5	2.5	0.0	0.0	0.0
69	0.0	0.0	0.1	0.0	0.0	0.2	0.1	0.1	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
70	0.7	0.9	1.4	0.4	0.5	1.1	0.0	0.0	0.5	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
71	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.8	0.0	0.0	0.0
72	0.0	0.1	0.3	0.0	0.0	0.0	0.1	0.1	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
73	0.5	0.7	1.3	0.6	1.0	2.6	0.2	0.3	1.9	0.0	0.0	0.0	0.8	1.7	1.7	0.0	0.0	0.0
81	0.0	0.0	0.0	0.0	0.0	0.4	0.0	0.0	0.1	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
82	0.6	0.7	1.3	1.0	1.3	2.5	0.8	1.0	1.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
82 (var IS39)	0.2	0.2	0.3	0.1	0.1	0.3	0.1	0.1	0.2	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
83	0.1	0.1	0.1	0.0	0.0	0.2	0.0	0.0	0.4	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
84	0.4	0.4	1.0	0.0	0.0	0.9	0.0	0.0	0.6	0.0	0.0	1.9	0.0	0.0	0.0	0.0	0.0	0.0
89	0.3	0.5	1.6	0.0	0.0	2.0	0.1	0.1	1.4	0.0	0.0	2.3	0.0	0.0	2.7	0.0	0.0	0.0
16, 18	5.6	9.3	11.8	24.1	36.7	39.6	40.6	56.1	58.0	62.2	87.6	87.9	56.1	67.7	67.9	32.6	36.4	36.7
6, 11, 16, 18	7.7	11.9	15.3	25.2	37.6	41.3	40.9	56.3	58.4	62.2	87.6	87.9	56.9	67.7	67.9	32.6	36.4	36.7
6, 11, 16, 18, 31, 33, 45, 52, 58	18.9	24.6	29.3	48.9	65.9	70.0	67.0	82.3	83.7	76.2	93.9	93.9	73.0	78.6	79.9	36.7	40.8	42.9
Alpha-3[h]	1.5	1.9	4.5	0.2	0.2	4.7	0.2	0.2	3.4	0.0	0.0	4.1	0.0	0.0	3.5	0.0	0.0	0.0
Alpha-5[h]	4.8	6.7	8.9	5.3	8.0	11.7	2.7	3.6	6.8	0.0	0.0	3.8	1.7	2.5	2.5	0.0	0.0	2.0
Alpha-6[h]	9.5	13.2	16.1	3.2	4.9	11.5	1.3	1.6	5.4	0.0	0.0	8.3	0.0	0.0	2.5	0.0	1.1	2.1
Alpha-7[h]	10.9	14.6	18.8	8.2	11.8	21.4	5.9	7.3	14.7	42.8	52.5	57.9	16.2	17.6	21.2	17.4	19.4	21.8
Alpha-9[h]	14.4	19.5	24.4	47.0	65.3	69.3	65.5	81.6	83.0	29.6	41.4	47.3	60.2	67.3	68.8	18.9	24.4	27.6
Alpha-10[h]	2.1	2.9	4.7	0.7	0.8	3.1	0.2	0.2	1.7	0.0	0.0	1.9	0.0	0.0	0.8	0.0	0.0	0.0
Alpha-11[h]	0.5	0.7	1.4	0.6	1.0	2.6	0.2	0.3	1.9	0.0	0.0	0.0	0.8	1.7	1.7	0.0	0.0	0.0
Any carcinogenic	35.0	42.5	45.7	68.0	83.6	85.3	79.7	90.8	91.3	81.8	93.9	93.9	79.7	86.6	87.4	42.8	43.9	44.9
Any noncarcinogenic	14.9	18.1	25.6	7.2	8.9	24.4	3.9	4.3	15.4	0.0	0.0	12.1	2.7	3.5	10.4	0.0	1.1	2.1

[a]CIN1 includes 249 diagnoses of low-grade lesion without specification of CIN.
[b]CIN2 includes 188 diagnoses of CIN1/2.
[c]CIN3 includes 69 diagnoses of high-grade lesion without specification of CIN, 475 diagnoses of CIN2/3, and 222 diagnoses of CIS.
[d]SCC includes 4 diagnoses of carcinoma without specification of histologic type.
[e]Minimum estimate of attribution.
[f]Proportional estimate of attribution.
[g]Maximum estimate of attribution.
[h]HPV alpha species: alpha-3 is hpv61, 62, 72, 81, 83, or 84; alpha-5 is hpv26, 51, 69, or 82; alpha-6 is hpv53, 56, or 66; alpha-7 is hpv18, 39, 45, 59, 68, or 70; alpha-9 is hpv16, 31, 33, 35, 52, 58, or 67; alpha-10 is hpv6, 11, 44, 55, or 74; alpha-11 is hpv34, 64, or 73.

longer to do so and occur more commonly at older ages, consistent with the weaker carcinogenic potential. Even HPV6 and 11 may in very rare circumstances cause cervical cancer (27). However, inclusion of low-risk or borderline carcinogenic types in any HPV screening test would significantly increase the test positivity with very small gains in sensitivity for precancerous lesions (28).

One limitation to this analysis is that we have not yet performed linkages to HPV vaccination status in this sample of the NM population, although work is currently ongoing to enable this evaluation. Undoubtedly, some women in this sample had undergone HPV vaccination during this time period (2006–2009). However, we believe that the impact on these results is minimal for the following reasons. First, the uptake of HPV

vaccination in the United States has been somewhat slow (29, 30). National survey-based data reported for 2012 suggest that approximately one third of adolescent girls ages 13 to 17 years received all three doses of the vaccine and approximately 53% received a single dose, similar to estimates specific to New Mexico (29). Second, the median age for a diagnosis of CIN2 in our population was 25 years, for CIN3 was 28 years, and for AIS was 35 years, well beyond the age when most women would have been vaccinated. Third, the older the woman is at the time of vaccination, the less benefit (on average) she gleans from it (31, 32) because HPV vaccination is prophylactic but not therapeutic and does not treat preexisting HPV infections and related conditions (33, 34). Most women in the target age range for HPV vaccination, ages 9 to 12 years, would probably not have undergone screening and would not have been captured in this population sample. The impact of unmeasured HPV vaccination would be expected to be greatest in women <21 years of age, a group of women who will no longer be screened according to current U.S. cervical cancer screening guidelines (12, 14). We have already observed a sharp decrease in screening in this age group (35). Although we reported the HPV genotype distribution in this age group for completeness, we anticipate that soon there will be very few women ages <21 years to study the impact of HPV vaccination in routine clinical screening (vs. clinical trials). Finally, our population-based evaluation included tissue specimens from biopsies taken before and immediately after initial HPV vaccine licensure in the United States and the impact of HPV vaccination on cervical precancer, even with high vaccine coverage, has both been shown and predicted to take several years to observe among women attending clinics for cervical screening (36–38).

We noted that the percentage of HPV positive (44.9%) among the 47 cases of ADC identified in this population sample was low, although the distribution of HPV genotypes among the HPV positives was as expected. That is, HPV16 and HPV18 cause about 80% of ADC (1). de Sanjose and colleagues (1) found that only 62% of the ADC tested HPV positive compared with 87% of the SCC . The higher percentage of ADC that were HPV positive in that study may be explained by the use of primers that target short fragments of the HPV L1 gene, and therefore may be less affected by the DNA degradation caused by formalin fixation (39). We previously performed a direct comparison in paraffin-embedded tissues of the LINEAR ARRAY HPV Genotyping test used in this study versus that used in the study of de Sanjose and found no substantial differences (2) . Our earlier study, however, conducted HPV genotyping in CIN3/CIS and invasive cervical cancers versus a population-based sample of CIN across all grades as we have currently done. It is possible that targeting HPV across the full spectrum of CIN grades using paraffin-embedded tissues might benefit from the use of amplification systems targeting shorter fragments.

The overall lower percentage of HPV-positive ADC in both studies compared with SCC suggests a possible systematic issue. Misclassification of HPV-negative endometrial cancers as cervical cancers is not uncommon (40–42), which contributes to the pool of HPV-negative ADC.

In conclusion, we have established the prevalence of HPV genotypes across the continuum of cervical diagnoses in this unique national surveillance resource using tissue-based HPV genotyping, the standard for HPV genotype attribution. The motivation for this baseline study was to establish HPV genotype prevalence for the types targeted by current and future HPV vaccines so that we can measure the population effectiveness of HPV vaccination over time and evaluate the performance of evolving cervical screening strategies. Monitoring the impact of these vaccines on the rates of cervical precancers and ultimately invasive cervical cancers, as well as any changes in the HPV types responsible for these cases over time, has high public health importance. As HPV vaccination data are linked to outcomes data, which are expected to begin in 2015, this resource can address a wide range of questions about HPV vaccination in the United States that are unlikely to be addressed in clinical trials, including the long-term effectiveness of one, two and three doses of HPV vaccines, the health economic benefits of HPV vaccination and the potential impact on cervical cancer screening program performance. The NMHPVPR is, to our knowledge, the only population-based resource in the United States outside of managed care organizations with the ability to link vaccination with changes in cervical screening, diagnosis, and treatment (34). This will be particularly important given the relatively low vaccine coverage in the United States.

Disclosure of Potential Conflicts of Interest

B.M. Ronnett is a consultant/advisory board member for Merck. M.H. Stoler is a consultant/advisory board member for Merck, Roche, Hologic/GenProbe, BD, Qiagen, Cepheid, and Inovio. P.E. Castle is a CEO at Global Coalition Against Cervical Cancer; an executive director at Global Cancer Initiative; has received speakers' bureau honoraria from Roche and Cepheid; and is a consultant/advisory board member for Roche, BD, Cepheid, Hologic, Merck, ClearPath, Guided Therapeutics, Inovio, and Teva Pharmaceuticals. C.M. Wheeler has provided expert testimony for Roche Molecular Systems. No potential conflicts of interest were disclosed by the other authors.

Disclaimer

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