Research Article

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Cervical Precancer and Cancer Risk by Human Papillomavirus Status and Cytologic Interpretation: Implications for Risk-Based Management

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Abstract

Background: Cervical cancer risks, estimated by using cervical intraepithelial neoplasia grade 3 (CIN3) or more severe diagnoses (≥CIN3) endpoints, have not been quantified for different combinations of results from currently approved screening methods. Understanding these risks will guide optimal patient management.

Methods: Women aged ≥25 years ($n = 7,823$) underwent high-risk human papillomavirus (hrHPV) and liquid-based cytology (LBC) testing. Women with hrHPV-positive results and/or abnormal LBC, plus a random subset of hrHPV and LBC negatives, underwent colposcopy; those without ≥CIN2 at baseline were screened annually by LBC and referred to colposcopy for an abnormal LBC ($n = 7,392$). One- and 3-year ≥CIN3 risks with 95% confidence intervals (95% CI) were calculated for paired hrHPV and LBC (hrHPV/LBC) results.

Results: One-year ≥CIN3 risks ranged from 81.27% (95% CI, 66.02%–90.65%) for HPV16 positive/high-grade to 0.33% (95% CI, 0.18%–0.62%) for hrHPV negative/negative for intraepithelial lesion or malignancy (NILM). One-year ≥CIN3 risk for HPV16/NILM (13.95%; 95% CI, 10.98%–17.58%) was greater than low-grade squamous intraepithelial lesion (LSIL; 7.90%; 95% CI, 5.99%–10.37%; $P = 0.002$) and similar to hrHPV-positive/LSIL (11.45%; 95% CI, 8.61%–15.07%; $P = 0.3$). Three-year ≥CIN3 risks for HPV16 positive/LSIL and HPV16/atypical squamous cells of undetermined significance was 24.79% (95% CI, 16.44%–35.58%) and 24.36% (95% CI, 15.86%–35.50%), respectively, and 0.72% (95% CI, 0.45%–1.14%) for hrHPV negative/NILM.

Conclusions: hrHPV and LBC results stratify cervical cancer risk by more than two orders of magnitude. HPV16-positive women, regardless of the LBC result, warrant immediate colposcopy. Women with concurrent HPV16 and high-grade LBC might consider treatment without a confirmatory biopsy with informed decision-making with their provider.

Impact: These results provide relevant benchmarks for risk-based cervical cancer screening and management. *Cancer Epidemiol Biomarkers Prev; 25(12); 1595–9. ©2016 AACR.*

Introduction

New cervical cancer screening guidelines and recommendations (1, 2) incorporate high-risk human papillomavirus (hrHPV) testing, thereby taking advantage of the excellent reassurance against cervical precancer [i.e., cervical intraepithelial neoplasia grade 2 (CIN2), grade 3 (CIN3), and adenocarcinoma *in situ* (AIS)] and invasive cervical cancer that a hrHPV-negative test provides (3). Management of screen positives (1, 4) depends on the specific screening modality (cytology and/or hrHPV testing) and whether the hrHPV test includes separate detection of HPV16 and HPV18 or HPV18 and HPV45 combined ("partial HPV genotyping"). However, exact risks for each screening combination are not well documented over sufficient follow-up to account for diagnostic inaccuracies. Previous studies have relied on research HPV assays and sampling and do not reflect current practice using FDA-approved assays. For example, data from the Portland Kaiser cohort relied on combining data from two research use–only assays conducted on cervicovaginal lavage (5, 6), none of which are in clinical practice now. In addition, although data from Kaiser Permanente Northern California (KPNC) have contributed greatly to current screening and management guidelines (4), currently, there are no partial HPV genotyping data available from KPNC. We therefore report the 1- and 3-year cumulative risks of ≥CIN3 (CIN3, AIS, or cervical cancer) and ≥CIN2 (CIN2 or ≥CIN3) of women aged ≥25 years participating in the follow-up phase of ATHENA.

Materials and Methods

The study methods and description of the population have been reported in detail elsewhere (7). The Institutional Review Boards of all participating clinical sites and institutions approved the study. All participants provided written informed consent.

Briefly, after providing a brief medical history, participants underwent a pelvic exam during which a cervical sample was collected and placed into a PreservCyt vial (Hologic, Inc.). Prior to

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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processing for liquid-based cytology (LBC; ThinPrep; Hologic), a 4-mL PreservCyt aliquot was removed for hrHPV testing using the analytically sensitive research HPV tests AMPLICOR and LINEAR ARRAY HPV Genotyping Test as well as the cobas HPV Test (Roche Molecular Systems). The cobas HPV Test provides three positive/negative results in three channels: HPV16, HPV18, and a pool of 12 other hrHPV genotypes. A fourth channel provides a read-out for β-globin as an internal control for the presence of human DNA (7). LBC results were reported as high-grade squamous intraepithelial lesion (HSIL), atypical squamous cells cannot rule out HSIL (ASC-H), atypical glandular cells (AGC) of unknown significance (AGUS), low-grade squamous intraepithelial lesion (LSIL), atypical squamous cells of undetermined significance (ASC-US), and negative for intraepithelial lesion or malignancy (NILM) (8). All women who had an abnormal LBC [ASC-US or worse (≥ASC-US)] and/or tested hrHPV positive by AMPLICOR or LINEAR ARRAY underwent colposcopy with biopsy and, in some patients, endocervical curettage (ECC) within 12 weeks of the initial visit; a subgroup of women with both hrHPV and LBC-negative results was also randomly selected for colposcopy. Colposcopists and patients were masked to the screening test results until after the colposcopy visit. A panel of three pathologists reviewed the biopsies and ECCs masked to patient information and screening test results (7).

These analyses included 7,823 women, including the 431 women diagnosed with ≥CIN2 at baseline and were exited from the study. Women who underwent colposcopy in the baseline phase and did not have ≥CIN2 were eligible for the 3-year follow-up phase ($n = 7{,}392$) as described previously (7). Women in the follow-up phase were screened annually by cervical cytology and hrHPV testing as performed by their clinic. Women with abnormal cytology (≥ASC-US) were referred to colposcopy with biopsy and/or ECC according to the same protocol utilized during the baseline phase. Women found to have a diagnosis of ≥CIN2 in follow-up were exited from the study. At year 3, patients were invited to have an "exit colposcopy" according to the same protocol at baseline and follow-up. Women who declined the exit colposcopy (319/4,663, 6.8%) had a cervical specimen collected for LBC and hrHPV testing.

We combined HSIL, ASC-H, or AGC/AGUS into a single "high-grade" LBC category due to small numbers of each. Conservatively, we did not calculate the corresponding 3-year risks for women with high-grade LBC due to the expected low numbers of these women returning for follow-up, resulting in unreliable estimates. hrHPV test results were classified positive and negative for hrHPV and hierarchically according to cancer risk (9): HPV16 positive, else HPV16 negative and HPV18 positive, else HPV16 and HPV18 negative and positive for the pool of 12 other hrHPV types, or hrHPV negative. Paired hrHPV and LBC test results are reported here using a convention of "hrHPV result/LBC result."

Cumulative incidence risk (CIR) over 1 or 3 years for the entire cohort of 7,823 was estimated using Kaplan–Meier method. That is, CIR represented baseline risk in the 431 women diagnosed with ≥CIN2 at baseline and the cumulative detection of disease after baseline over 1 and 3 years of follow-up for the 7,392 women who did not have ≥CIN2 at baseline. Approximate pointwise confidence intervals (CI) were computed as in the work of Meeker and Escobar (10). Results were confirmed using Weibull models as described previously (data not shown; ref. 11).

Results

Over the 3-year follow-up (Supplementary Table S1), 347 women were diagnosed with ≥CIN3, of which 167 (48.1%) were hrHPV and LBC positive, 146 (42.1%) were hrHPV positive only, 16 (4.6%) were LBC positive only, and 18 (5.2%) were hrHPV and LBC negative at baseline. Among the 347 ≥CIN3 cases, 73 (21.0%) were diagnosed in follow-up, of which at baseline 34 (46.6%) were hrHPV and LBC positive, 27 (37.0%) were hrHPV positive only, 3 (4.1%) were LBC positive only, and 9 (12.3%) were hrHPV and LBC negative. A diagnosis of ≥CIN2 was made in 587 women, of which 252 (42.9%) were hrHPV and LBC positive, 252 (42.9%) were hrHPV positive only, 33 (5.6%) were LBC positive only, and 50 (8.5%) were hrHPV and LBC negative at baseline. Of the 587 ≥CIN3 cases, 156 (26.6%) were diagnosed in follow-up, of which 52 (33.3%) were hrHPV and LBC positive, 72 (46.2%) were hrHPV positive only, 11 (7.1%) were LBC positive only, and 21 (13.5%) were hrHPV negative and LBC negative at baseline.

Table 1 shows the 1-year risks of ≥CIN3 and ≥CIN2. One-year ≥CIN3 risks ranged from lows of 0.31% (95% CI, 0.10%–0.96%) for women with hrHPV negative/ASC-US and 0.33% (95% CI, 0.18%–0.62%) for women with hrHPV negative/NILM to a high of 81.27% (95% CI, 66.02%–90.65%) for women with HPV16 positive/high-grade. Women with HPV16 positive/NILM (13.95%, 95% CI, 10.98%–17.58%) had a greater 1-year ≥CIN3 risk than LSIL (7.90%; 95% CI, 5.99%–10.37%; $P = 0.002$), a benchmark for referral to colposcopy (4), and had a comparable 1-year ≥CIN3 risk to hrHPV positive/LSIL (11.45%; 95% CI, 8.61%–15.07%; $P = 0.3$). In comparison, the 1-year ≥CIN3 risk for hrHPV negative/LSIL was 1.35% (95% CI, 0.43%–4.09%).

The 1-year ≥CIN3 risk for HPV18 positives (10.28%) was comparable with LSIL (7.90%; $P = 0.25$) and was 2-fold higher than those positive for the 12 other hrHPV types (4.83%; $P < 0.001$). However, the 1-year ≥CIN3 risk for HPV18 positive/NILM (4.8%) was nonsignificantly less than for LSIL ($P = 0.15$).

Table 2 shows the 3-year risks of ≥CIN3 and ≥CIN2. The 3-year ≥CIN3 risks ranged from a low of 0.72% (95% CI, 0.45%–1.14%) for hrHPV negative/NILM and 0.46% (95% CI, 0.17%–1.23%) for HPV negative/ASC-US to a high of 24.79% (95% CI, 16.44%–35.58%) for HPV16 positive/LSIL. Women with HPV16 positive/NILM (17.43%, 95% CI, 13.90%–21.63%) had a greater 3-year ≥CIN3 risk than LSIL (8.67%; 95% CI, 6.61%–11.29%; $P < 0.001$) and marginally greater 3-year ≥CIN3 risk than hrHPV positive/LSIL (12.28%; 95% CI, 9.28%–16.08%). One- and 3-year ≥CIN2 risks showed similar patterns of risk stratification by HPV and LBC testing results as the ≥CIN3 risks.

Discussion

In the largest U.S. clinical trial of hrHPV testing to date, we demonstrated that routine, clinically available data from hrHPV testing with partial HPV genotyping and LBC can effectively stratify the population for cervical cancer risk, as best represented by ≥CIN3, by more than two orders of magnitude. hrHPV testing identifies a larger group of women with or at risk of ≥CIN3 than LBC alone, and hrHPV and LBC "cotesting" identifies only a small additional group (∼5%) of women with or at risk of ≥CIN3 compared with hrHPV testing

Table 1. One-year risks of ≥CIN2 and ≥CIN3 by pairwise combinations of hrHPV and LBC test results

		Baseline LBC result									
		HSIL[a]		LSIL		ASC-US		NILM		All	
Baseline cobas testing result[b]	Diagnosis	*n*	CIR (95% CI)	*n*	CIR (95% CI)	*n*	CIR (95% CI)	*n*	CIR (95% CI)	*n*	CIR (95% CI)
All hrHPV positive	≥CIN3	131	63.79 (53.91–72.63)	433	11.45 (8.61–15.07)	376	11.39 (8.44–15.21)	2,562	5.19 (4.38–6.13)	3,502	8.64 (7.73–9.64)
	≥CIN2		71.37 (62.16–79.10)		21.84 (18.04–26.18)		16.98 (13.41–21.26)		8.61 (7.56–9.78)		13.38 (12.26–14.58)
HPV16 positive	≥CIN3	69	81.27 (66.02–90.65)	99	22.87 (15.04–33.18)	85	22.14 (14.32–32.59)	440	13.95 (10.98–17.58)	693	21.99 (18.96–25.34)
	≥CIN2		83.33 (69.45–91.67)		37.85 (28.38–48.34)		30.88 (21.93–41.54)		18.42 (15.01–22.39)		28.56 (25.24–32.13)
HPV18 positive	≥CIN3	15	66.67 (40.60–85.40)	33	12.73 (4.83–29.53)	36	14.00 (5.30–32.12)	189	4.76 (2.50–8.90)	273	10.28 (7.13–14.61)
	≥CIN2		73.33 (46.69–89.62)		15.78 (6.69–32.89)		17.74 (7.52–36.37)		9.50 (5.97–14.80)		14.73 (10.88–19.64)
12 other hrHPV positive	≥CIN3	47	42.13 (27.78–57.94)	301	7.60 (4.97–11.46)	255	7.46 (4.73–11.57)	1,933	3.23 (2.52–4.14)	2,536	4.83 (4.05–5.77)
	≥CIN2		56.91 (41.54–71.06)		17.20 (13.20–22.10)		12.32 (8.73–17.12)		6.29 (5.27–7.49)		9.08 (8.00–10.30)
hrHPV negative	≥CIN3	56	14.93 (7.59–27.27)	223	1.35 (0.43–4.09)	967	0.31 (0.10–0.96)	3,075[c]	0.33 (0.18–0.62)	4,321	0.56 (0.38–0.84)
	≥CIN2		16.67 (8.85–29.16)		3.70 (1.86–7.24)		0.85 (0.42–1.69)		1.14 (0.81–1.59)		1.40 (1.09–1.81)
All	≥CIN3	187	48.22 (40.56–55.97)	656	7.90 (5.99–10.37)	1,343	3.34 (2.48–4.48)	5,634	2.53 (2.15–2.98)	7,823	4.15 (3.73–4.63)
	≥CIN2		54.55 (46.92–61.96)		15.60 (12.93–18.70)		5.31 (4.21–6.68)		4.52 (4.00–5.11)		6.74 (6.19–7.33)

NOTE: A total of 7,823 women, those censored at baseline because of ≥CIN2 diagnosis ($n = 431$) plus those without CIN2 who entered the 3-year follow-up phase of the study ($n = 7,392$), were included in these analyses. Absolute risks of ≥CIN3 and ≥CIN2 for each combination of Pap and HPV test results for each year was calculated as the proportion of women with ≥CIN3 or ≥CIN2 diagnoses, respectively, among the number of women at risk for that year.

[a]HSIL, ASC-H, or AGC/atypical glandular cells of undetermined significance.

[b]hrHPV testing results were ranked hierarchically according to cancer risk (HPV16 positive, else HPV16 negative and HPV18 positive, else HPV16 and HPV18 negative and positive for the pool of 12 other hrHPV types, or hrHPV negative; ref. 9).

[c]Random sample of all women with hrHPV negative and NILM LBC.

alone. Women with hrHPV negative/ASC-US or hrHPV negative/NILM were at the lowest and similar risks, again raising the question of the appropriate follow-up of hrHPV-negative/ASC-US women (1, 4, 12).

Among women with NILM, HPV18-positive women did not have sufficient risk to warrant colposcopy based on current benchmarks of risk (4) and were not distinguishable from the risk for women testing positive for the pool of the 12 other hrHPV. The apparent contradiction between these and other results (13) for HPV18-positive ≥CIN3 risks and the overwhelming evidence that HPV18 is the second leading cause of cervical cancer after HPV16 (9) may be the result of difficulties in identifying HPV18-related CIN3, as has been previously discussed (14). It is worth noting that HPV18 is an equally important cause as HPV16 of cervical adenocarcinoma (9), which is on the rise in most western countries (15). This is presumably due to the increased exposure to HPV several decades ago (16) and poorer detection of the precursors of cervical adenocarcinoma than squamous cell carcinoma by cytology (11). Given the importance of identifying women at risk for invasive cervical cancer ultimately to prevent it, we suggest that separate HPV18 detection is useful despite its comparable ≥CIN3 risk with the other 12 hrHPV types in aggregate as HPV18-positive CIN3 must be a more important cause of cervical cancer than CIN3 caused by the 12 other hrHPV types individually (17).

Women with HPV16, regardless of cytologic result, resulted in ≥CIN3 risks (≥13.95% and ≥17.93% 1- and 3-year, respectively) that exceed the ≥CIN3 risk for women with LSIL cytology unqualified by HPV status (7.90% and 8.67% 1- and 3-year, respectively). LSIL has been the traditional risk threshold for referral to colposcopy in the United States (4, 18, 19) and, therefore, is considered the benchmark for colposcopic referral (20). In the era of HPV and Pap cotesting, it is preferred that only hrHPV-positive LSIL women are sent to colposcopy. The 3-year risks of ≥CIN3 for HPV16 positive/NILM were marginally greater than that of hrHPV-positive/LSIL. Thus, a woman with a HPV16-positive result could be referred to colposcopy immediately without waiting for the cytology results. This confirms the previous longitudinal results (5, 6, 21).

Women with HPV16 positive/high-grade were at the highest risk and had a very high probability of ≥CIN3 within a few years; although we could not estimate the risk after one year, additional women did return with CIN3 and CIN2 (data not shown), suggesting that the risk approaches unity. Given the imperfect sensitivity of colposcopically directed biopsies as typically practiced (22), women with HPV16-positive/high-grade cytology, especially those with HPV16-positive HSIL, might undergo excisional treatment without confirmatory biopsy for the ≥CIN3 that almost certainly is there. Given the 1-year risks of ≥CIN3 for HPV16 positive/high-grade is almost twice that of high-grade LBC (81.27% vs. 48.22%, respectively), it is reasonable to expect that HPV16 positive/HSIL is almost twice that of HSIL LBC. Already, women with HSIL unqualified by hrHPV testing results can undergo treatment without confirmatory biopsy of ≥CIN2 (4).

Such an approach of treating HPV16 positive/high-grade, especially HPV16 positive/HSIL, would reduce losses to follow-up to completing care, health care costs, and financial and psychosocial burdens to the patient with little chance of unnecessary treatment. Yet such a decision would be best done as informed decision with

Table 2. Three-year risks of ≥CIN2 and ≥CIN3 by pairwise combinations of hrHPV and LBC test results

Baseline cobas testing result[b]	Diagnosis	Baseline LBC result: HSIL[a] *n*	HSIL[a] CIR (95% CI)	LSIL *n*	LSIL CIR (95% CI)	ASC-US *n*	ASC-US CIR (95% CI)	NILM *n*	NILM CIR (95% CI)	All *n*	All CIR (95% CI)
All hrHPV positive	≥CIN3	Not reported		433	12.28 (9.28–16.08)	376	12.70 (9.50–16.79)	2,562	6.20 (5.28–7.27)	3,502	9.68 (8.69–10.77)
	≥CIN2				23.67 (19.66–28.22)		19.80 (15.84–24.46)		10.99 (9.74–12.37)		15.75 (14.50–17.08)
HPV16 positive	≥CIN3			99	24.79 (16.44–35.58)	85	24.36 (15.86–35.50)	440	17.43 (13.90–21.63)	693	25.07 (21.73–28.74)
	≥CIN2				40.96 (31.02–51.69)		32.86 (23.44–43.89)		23.45 (19.42–28.02)		32.75 (29.11–36.60)
HPV18 positive	≥CIN3			33	12.73 (4.83–29.53)	36	14.00 (5.30–32.12)	189	5.72 (3.05–10.48)	273	10.97 (7.63–15.53)
	≥CIN2				15.78 (6.69–32.89)		17.74 (7.52–36.37)		12.09 (7.84–18.19)		17.13 (12.82–22.51)
12 other hrHPV positive	≥CIN3			301	8.19 (5.40–12.25)	255	8.71 (5.64–13.22)	1,933	3.72 (2.93–4.72)	2,536	5.40 (4.54–6.41)
	≥CIN2				18.79 (14.53–23.95)		15.88 (11.59–21.37)		8.06 (6.84–9.47)		10.97 (9.73–12.34)
hrHPV negative	≥CIN3			223	2.01 (0.74–5.31)	967	0.46 (0.17–1.23)	3,073[c]	0.72 (0.45–1.14)	4,321	0.91 (0.64–1.27)
	≥CIN2				4.35 (2.26–8.19)		1.90 (1.14–3.16)		1.90 (1.44–2.51)		2.21 (1.78–2.75)
All	≥CIN3	Not reported		656	8.67 (6.61–11.29)	1,343	3.79 (2.85–5.02)	5,634	3.19 (2.74–3.72)	7,823	4.79 (4.31–5.31)
	≥CIN2				17.00 (14.17–20.26)		6.84 (5.53–8.43)		6.00 (5.36–6.70)		8.22 (7.60–8.89)

NOTE: A total of 7,823 women, those censored at baseline because of ≥CIN2 diagnosis ($n = 431$) plus those without CIN2 who entered the 3-year follow-up phase of the study ($n = 7{,}392$), were included in these analyses. Absolute risks of ≥CIN3 and ≥CIN2 for each combination of Pap and HPV test results for each year was calculated as the proportion of women with ≥CIN3 or ≥CIN2 diagnoses, respectively, among the number of women at risk for that year. Calculations for 3-year risks for high-grade LBC for the different category of hrHPV results were not reported because of small numbers of women with high-grade cytology in those HPV categories (5 and 5 for HPV16, 2 and 0 for HPV18, and 11 and 11 for other hrHPV, and 30 and 24 for hrHPV negative for years 2 and 3, respectively) returning after one year.

[a]HSIL, ASC-H, or AGC/atypical glandular cells of undetermined significance.

[b]hrHPV testing results were ranked hierarchically according to cancer risk: (HPV16 positive, else HPV16 negative and HPV18 positive, else HPV16 and HPV18 negative and positive for the pool of 12 other hrHPV types, or hrHPV negative; ref. 9).

[c]Random sample of all women with hrHPV negative and NILM LBC.

provider, given the possible relationship of excisional treatments and negative reproductive outcomes, including preterm delivery (23–25).

There were a number of limitations in this study that bear mentioning. First, the aggressive colposcopy protocol likely resulted in earlier identification of CIN3 and CIN2, some of the latter of which might have regressed spontaneously in a year or two (26, 27). For that reason, we relied on ≥CIN3, which is much less regressive, as our primary endpoint. Second, these results need to be replicated given the small numbers and unstable estimates for some of the clinically important combinations of hrHPV testing and cytologic results. Finally, some CIN2 and CIN3 were found by blind biopsy, the clinical significance of which is uncertain. However, a recent study reported that the CIN2/3 biopsies from directed and random biopsies were equally likely to stain positive for $p16^{INK4a}$ (28), which suggests that they are biologically similar.

Finally, as previously suggested (29), there is an increasing complexity in cervical cancer screening and management due to the numerous combinations of clinical results as well as the potential for differences in *a priori* risks due to screening and vaccination history and age. In addition, new biomarkers may soon be incorporated into routine clinical practice (30). Although there are only five possible clinical actions based on risk bands, screening, increased surveillance, colposcopy, treatment, and exit screening, there are many combinations that can lead to these risks. A clinical algorithm for every clinically meaningful combination of test or diagnostic results is no longer practical. A risk estimation tool, based on the best available population data to estimate risks accurately, is needed in which the patient information that is available can be quickly and easily entered, preferably directly from the electronic medical records database, and the output is the appropriate clinical management. Although decision support tools exist, including one developed by the American Society for Colposcopy and Cervical Pathology, the latter is still based fundamentally on clinical algorithms, and it is unknown how well these tools support the general and/or nonacademic busy practitioner whose starting knowledge of current guidelines may be much less that the academician gynecologist. Thus, an important future goal, in addition to improving upon the risk estimation for more personalized management and improved benefits to harms, is a simple, clear, and direct communication of the recommended clinical actions based on the risk to providers and patients to improve compliance.

Disclosure of Potential Conflicts of Interest

P.E. Castle has received speakers bureau honoraria from Cepheid and Roche and is a consultant/advisory board member for Cepheid, ClearPath, GE Healthcare, GenProbe/Hologic, Genticel, Guided Therapeutics, Inovio, Merck, Roche, and Teva. S. Aslam is the principal biostatistician at Roche. C. Behrens is a senior director (Clinical Research) at Roche Molecular Systems and is a consultant/advisory board member for Antiva Biosciences. No other potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: P.E. Castle, C. Behrens
Development of methodology: C. Behrens
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): C. Behrens
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): P.E. Castle, S. Aslam, C. Behrens
Writing, review, and/or revision of the manuscript: P.E. Castle, S. Aslam, C. Behrens
Study supervision: C. Behrens

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