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A Comparison of High-Grade Cervical Abnormality Risks in Women Living with and without Human Immunodeficiency Virus Undergoing Routine Cervical-Cancer Screening

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Abstract

As the US moves increasingly towards using human papillomavirus (HPV) testing with or without concurrent cytology for cervical cancer screening, it is unknown what the corresponding risks are following a screening result for women living with HIV (WLWH), which will dictate the optimal clinical follow-up. Therefore, using medical records data from Kaiser Permanente Northern California, which introduced triennial HPV and cytology co-testing in women aged 30–64 years in 2003, we compared risks of cervical intraepithelial neoplasia grade 2 (CIN2) or more severe diagnoses (CIN2+) in women not known to have HIV (HIV[−] women) (n=67,488) frequency matched 111:1 on age and year of the first co-test to the 608 WLWH (n=608). WLWH were more likely to test HPV positive (20.2% vs. 6.5%, p<0.001) and have non-normal cytology (14.1% vs. 4.1%, p<0.001) than HIV[−] women. Five-year CIN2+ risks for all WLWH and HIV[−] women were 3.5% (95%CI=2.0–5.0%) and 1.6% (95%CI=1.5–1.8%) (p=0.01), respectively. Five-year CIN2+ risks for WLWH with positive HPV and non-normal cytology, positive HPV and normal cytology, negative HPV and non-normal cytology, and negative HPV and normal cytology

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Declaration of interests

Dr. Castle has received HPV tests and assays for research at a reduced or no cost from Roche, Becton Dickinson, Cepheid, and Arbor Vita Corporation.

were 24.9% (95%CI=13.4–36.4%), 3.0% (95%CI=0.0–7.4%), 3.6 (95%CI=0.0–9.8%) and 0.3% (95%CI=0.0–0.8%), respectively. Corresponding 5-year CIN2+ risks for HIV[−] women were 26.6% (95%CI=24.6–28.7%), 8.5% (95%CI=7.2–9.9%), 1.9% (95%CI=1.0–2.8%), and 0.5% (95%CI=0.4–0.6%), respectively. Thus, in this healthcare setting, the main cause in overall CIN2+ risk differences between WLWH and HIV[−] women was the former was more likely to screen positive and once the screening result is known, it may be reasonable to manage both populations similarly.

Keywords

Human papillomavirus (HPV); cytology; Pap; cervical intraepithelial neoplasia; cervical cancer; human immunodeficiency virus (HIV)

Introduction

Current cervical-cancer screening recommendations are (Curry et al., 2018): 1) triennial cytology screening for women aged 21–64 years, and 2) human papillomavirus (HPV) testing alone or concurrently with cytology (“co-testing”) every 5 years or triennial cervical cytology screening for women aged 30–64 years. Due to their greater overall cervical-cancer risk (Grulich et al., 2007; Silverberg and al, 2015; Stelzle et al., 2021), separate guidelines have been establish for women living with human immunodeficiency virus (HIV) (WLWH) (2021): 1) annual cytology, and following 3 negative results, triennial cytology for WLWH aged 21–29 years, and 2) triennial co-testing or annual cytology, and following 3 negative results, triennial cytology for WLWH aged ≥30 years.

There are few data on co-testing of WLWH. One observational cohort reported risks of cervical intraepithelial neoplasia (CIN) grade 2 (CIN2) or more severe diagnoses (CIN2+), stratified by HPV and cytology results, to be similar between WLWH and HIV[−] women (Keller et al., 2015; Keller et al., 2012). However, these results were observational in WLWH who were undergoing routine cervical cytology every 6- to 12-months, do not reflect those outcomes following routine co-testing and care, and the HIV[−] women in that study were selected to be at high risk for HIV. We therefore updated our previous analysis (Castle et al., 2012) to compare cervical outcomes in WLWH to an unselected population of HIV[−] women undergoing routine co-testing in the same managed healthcare system.

Methods

Study Population.

The Kaiser Permanente Northern California (KPNC) cohort consist of approximately 2.3 million women, approximately 1.6 million aged 30–64 years, enrolled in screening from January 1, 2003 to February 21, 2021. This cohort has been extensively described (Katki et al., 2011). KPNC screened women aged 30–64 years by HPV and cytology co-testing (and women aged 21–29 with cytology alone) until 2013, when it lowered the co-testing screening age to 25 years. The KPNC institutional review board approved use of the data,

and National Institutes of Health Office of Human Subjects Research deemed this study exempt from review.

Screening and Clinical Management.

Women were screened by HPV and Pap/cervical cytology co-testing as previously described (Gage et al., 2014; Katki et al., 2011). Women with abnormal screening tests and diagnoses were managed generally in accordance with national recommendations during that period.

Statistical methods.

To estimate relative risks, we frequency matched women not known to have HIV (HIV[−] women) to WLWH on exact year of age and calendar year of first co-test. Both relative and absolute risks of CIN2+ or CIN grade 3 or more severe diagnoses (CIN3+) were estimated using prevalence-incidence mixture models (Cheung et al., 2017; Hyun et al., 2017). These models combine a logistic regression model for prevalent high-grade cervical abnormalities and a proportional hazards model for incident high-grade cervical abnormalities, while accounting for delayed detection of prevalent high-grade cervical abnormalities due to colposcopy protocols (left censoring) and time of onset of incident high-grade cervical abnormalities occurring between two assessment visits (interval censoring). Women who are not cases (detected with CIN2+ or CIN3+ according to the analysis) were right censored at the time of their last negative assessment visit, which is defined as having <CIN2 histology or having a negative co-test result. Women who were not cases and had no negative assessment visit did not contribute to risk estimation (i.e., they are non-informative for the maximum likelihood estimation). An example of an individual not used to estimate risk is a woman testing HPV+/LSIL that did not attend colposcopy or have further follow-up visits. For women who had their first co-test less than 5 years from the final date of this dataset, they contributed to the risk estimates as either cases or right-censored controls. Even without follow-up beyond one visit (plus colposcopy, if applicable), they contribute to the immediate risk estimate, which is part of the 5-year cumulative risk estimate.

Both relative and absolute risk estimates of high-grade cervical abnormalities associated with HIV were adjusted for HPV status and cytology. We considered HPV-positive atypical squamous cells of undetermined significance, low-grade squamous intraepithelial lesion, or more severe cytologic interpretations as a positive (non-normal) cytology.

We calculated cumulative incidence (risk) of high-grade cervical abnormalities out to 5 years for the matched cohorts adjusting for HPV and cytology, then calculated weighted risk overall and stratified on HPV and cytology results. Although presented absolute risks for HIV-negative were estimated from the subset of matched controls, results agree with risks estimated from the full HIV-negative KPNC population (data not shown). Due to lack of CIN3+ cases among HPV-negative WLWH, we subsetted those models by HPV status to estimate the HPV-positive cumulative risk. The associated lack of standard errors prohibited us from calculating weighted risk estimates, instead we report marginal results in the overall and stratified results. All analysis were run in R 4.1.2. P of <0.05 was considered statistically significant.

Results

Seven hundred sixty-eight WLWH were identified, of which 674 (87.8%) had follow-up. Among those with follow-up, 556 (82.5%) had prevalent HIV at the time of the first co-test identified. Another 118 (17.5%) women were diagnosed with HIV after they became KPNC members, and their index co-test was the co-test after becoming HIV positive. Six hundred eight (90.8%) were in the age range of 30–64 years for routine screening by co-testing and were included in this analysis. HIV[−] women were matched 111:1 on age and year of the first co-test to the 608 WLWH, generating an HIV[−] sample of 67,488 women.

The median and mean age at time at index screen was 44 and 44.56 years, respectively. The distribution of year of first co-test was 20.2% for 2003–7, 28.6% for 2008–12, 31.9% for 2013–17, and 19.2% for 2018 or later. There was a significant difference in the racial composition of the two ($p<0.001$), with black being the most common race among WLWH (40.8%) and white being the most common race among the HIV[−] women (34.8%) (Table 1). WLWH were more likely than HIV[−] women to test HPV positive (20.2% vs. 6.5%, respectively, $p<0.001$) and have non-normal cytology (14.1% vs. 4.1%, respectively, $p<0.001$). WLWH also had many more visits than HIV[−] ($p<0.001$), which could not be explained by screening results (data not shown).

CIN2+ and CIN3+ risks by HIV status and baseline screening results are shown in Table 2. Five-year CIN2+ risks for all WLWH and HIV[−] women were 3.5% (95%CI=2.0–5.0%) and 1.6% (95%CI=1.5–1.8%) ($p=0.01$), respectively. Five-year cumulative CIN3+ risks for all WLWH and HIV[−] women were 1.3% (95%CI=0.3–2.3%) and 0.7 (95%CI=0.6–038%) ($p=0.24$), respectively.

Five-year CIN2+ risks following a positive HPV test were 15.6% (95%CI=8.7–22.5%) for WLWH and 17.9% (95%=16.6–19.1%) for HIV[−] women ($p=0.53$). Five-year CIN2+ risks following a negative HPV test were 0.4% (95%CI=0.0–0.9%) for WLWH and 0.5% (95%=0.4–0.6%) for HIV[−] women ($p=0.76$).

Five-year CIN2+ risks following non-normal cytology were 22.0% (95%CI=12.0–32.0%) for WLWH and 23.5% (95%CI=21.7–25.3%) for HIV[−] women ($p=0.77$). Five-year CIN2+ risks for normal cytology were 0.6% (95%CI=0.0–1.1%) for WLWH and 0.8% (95%CI=0.7–0.8%) for HIV[−] women ($p=0.50$).

Five-year CIN2+ risks for WLWH with positive HPV and non-normal cytology, positive HPV and normal cytology, negative HPV and non-normal cytology, and negative HPV and normal cytology were 24.9% (95%CI=13.4–36.4%), 3.0% (95%CI=0.0–7.4%), 3.6 (95%CI=0.0–9.8%) and 0.3% (95%CI=0.0–0.8%), respectively. Corresponding 5-year CIN2+ risks for HIV[−] women were 26.6% (95%CI=24.6–28.7%), 8.5% (95%CI=7.2–9.9%), 1.9% (95%CI=1.0–2.8%), and 0.5% (95%CI=0.4–0.6%), respectively. Notably, HPV-positive, cytology-negative HIV[−] women had significantly higher 5-year cumulative CIN2+ risk than WLWH (8.5% vs. 3.0%, respectively, $p=0.02$).

We used a logistic regression and cox proportional hazard model to test whether HIV was an independent risk factor for prevalent and incident CIN2+, respectively, after controlling

for HPV and cytology results. Being HIV positive (vs. negative) was neither associated with prevalent (OR=0.8, 95%CI=0.3–1.3) nor incident (HR=0.9, 95%CI=0.3–1.4) CIN2+. Positive (vs. negative) cytology (OR=9.5, 95%CI=3.3–15.7) and positive (vs. negative) HPV (OR=18.4, 95%=6.3–30.6) results were associated with prevalent CIN2+. Likewise, positive (vs. negative) cytology (HR=1.6, 95%CI=1.0–2.1) and positive (vs. negative) HPV (HR=16.4, 95%=11.3–21.5) results were associated with incident CIN2+.

Discussion

WLWH in this cohort were at approximately twice the risk of CIN2+ over a 5-year period compared to HIV[−] women primarily because they were much more likely to have a positive HPV and/or non-normal cytology result. That is, WLWH had greater carriage of HPV than HIV[−] women. Once stratified on (controlling for) screening results, CIN2+ risks were comparable between groups and therefore might be managed similarly, according to the principle of equal management for equal risk (Perkins et al., 2020). Importantly, CIN2+ risks, a proxy for cancer risk, following negative screening results appeared comparable. We suggest that screening intervals following a negative co-test- or HPV test for this population of WLWH, who are likely to have been previously well screened and their HIV infection well managed, might be extended safely. Extending screening intervals will reduce unnecessary screening and care, including treatment of regressive abnormalities, and associated costs. Cervical treatment has been linked to negative reproductive outcomes e.g., preterm delivery (Kyrgiou et al., 2016).

We acknowledge several limitations of this analysis. The relatively small sample size of WLWH required us to use CIN2+ rather than CIN3+ as our primary endpoint. CIN2 is an equivocal high-grade cervical abnormality, likely an admixture CIN3 and HPV infection. Compared with CIN3, CIN2 is poorly reproducible (Carreon et al., 2007; Stoler and Schiffman, 2001), has a distribution of HPV types that in toto is less risky (Castle et al., 2020), and commonly regresses especially in young women (Tainio et al., 2018). Even so, we are underpowered to detect small differences in risk between the two populations. We did not have data on the current and past HIV status e.g., HIV viral load or CD4 counts. Given the high quality of care at KPNC, we assume that most WLWH were receiving standard-of-care therapy for their HIV infection and therefore likely to have low if not undetectable HIV carriage and be in good health.

Finally, despite national and KPNC guidelines on co-testing for cervical-cancer screening of WLWH, these WLWH were screened much more frequently than HIV[−] women. This may have resulted in diagnosing more, regressive CIN2 while possibly censoring some CIN2 that might have been diagnosed eventually as CIN3.

We hypothesize that overscreening of WLWH is a common practice in the US, given the general knowledge of their increased cervical cancer, not accounting for well-screened populations of WLWH with good HIV control. Medicolegal concerns and frequent HIV-care visits of every 6 months may also influence the frequency of cervical-cancer screening in WLWH. However, these and other data (Keller et al., 2015; Keller et al., 2012) support the de-implementation of frequent cervical screening of those WLWH whose cervical cancer

risks and HIV infection are likely well managed, especially in WLWH still considering childbearing because of the potentially avoidable reproductive harms (Kyrgiou et al., 2016) that might result from overscreening. Research is needed to assess benefits, harms, and acceptability of extending screening intervals in comparable WLWH.

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Table 1.

Characteristics of study populations of women living with human immunodeficiency virus (HIV) (WLWH) matched with those who were not (HIV[−] women).

	HIV[−] Women (n=67,488)		WLWH (n=608)		
	n	**%**	**n**	**%**	**P**
Race					
Missing/Unknown	18,727	27.7	58	9.5	<0.001
White	23,489	34.8	160	26.3	
Black	3,976	6.9	248	40.8	
Asian/Pacific Islander	10,911	16.2	51	8.4	
Hispanic	9,224	13.7	73	12.1	
Native American	273	0.4	4	0.7	
Other	888	1.3	14	2.3	
HPV Results					
Positive	4,355	6.5	123	20.2	<0.001
Negative	6,1966	91.8	475	78.1	
Missing	11,167	1.7	10	1.6	
Cytology Results					
Non-normal	2,615	3.9	84	13.8	<0.001
Normal *	64,713	95.9	522	85.9	
Missing	160	0.2	2	0.3	
High-Grade **	547	0.8	9	1.5	<0.001
Low-Grade	2,068	3.1	75	12.3	
Negative *	64,713	95.9	522	85.9	
Missing	160	0.2	2	0.3	
Number of follow-up visits					
1	28,834	42.7	146	24.0	<0.001
2	15,173	22.5	100	16.4	
3	8,972	13.2	78	12.8	
4	6,775	10.0	63	10.4	
5	4,301	6.4	70	11.5	
≥6	3,433	5.1	151	24.8	

* Included atypical squamous cells of undetermined significance if the concurrent HPV test was negative.

** Included cancer, high-grade squamous intraepithelial lesion (HSIL, atypical squamous cells cannot rule out HSIL, and atypical glandular cells.

Table 2.

A comparison of cervical intraepithelial neoplasia grade 2 or more severe diagnoses (CIN2+) or grade 3 or more severe diagnoses (CIN3+) risks with 95% confidence intervals (95%CI) in women living with HIV (WLWH) and without HIV (HIV[−]), stratified on human papillomavirus (HPV) and cytology co-testing results. The first two row are the total population of WLWH and HIV[−] women. Risk estimates for paired WLWH and HIV[−] groups in which there were fewer than 30 WLWH and no cases of CIN2+ for those WLWH are not included. “Any” is for any result e.g., positive (Pos), negative (Neg), or not available (n/a).

HIV Status	HPV Result	Cytology Result	N_{Total}	$N_{informative}$ **	End point	N_{Cases}	Immediate (Prevalent)		1-Year Cumulative Risk		3-Year Cumulative Risk		5-Year Cumulative Risk		pCIN2+ † / p
							Risk (%)	95%CI (%)	Risk (%)	95%CI (%)	Risk (%)	95%CI (%)	Risk (%)	95%CI (%)	/
WLWH	Any	Any	608	474	CIN2+	22	2.4	1.2–3.5	2.6	1.4–3.9	3.1	1.8–4.4	3.5	2.0–5.0	
					CIN3+ §	7	0.8	0.0–1.6	0.9	0.0–1.7	1.0	0.2–1.8	1.3	0.3–2.3	0.01 / 0.
HIV [−]			67,488	39,398	CIN2+	907	0.8	0.7–0.9	1.2	1.1–1.3	1.4	1.3–1.5	1.6	1.5–1.8	
					CIN3+	377	0.4	0.4–0.5	0.5	0.5–0.6	0.7	0.6–0.7	0.7	0.6–0.8	
WLWH	Pos	Any	123	111	CIN2+	20	10.5	5.1–16	11.9	6.2–17.6	13.4	7.4–19.5	15.6	8.7–22.5	
					CIN3+	7	3.6	0.2–7	3.6	0.2–7	4.3	0.6–7.9	5.8	1.0–10.6	0.53 / 0.
HIV [−]			4355	3712	CIN2+	665	11.2	10–12.4	13.8	12.7–14.8	16.2	15–17.3	17.9	16.6–19.1	
					CIN3+	298	5.4	4.5–6.2	6.6	5.8–7.3	7.4	6.6–8.2	8.0	7.1–8.9	
WLWH	Neg		475	355	CIN2+	2	0.2	0–0.7	0.2	0–0.7	0.4	0–0.8	0.4	0–0.9	
					CIN3+ §	0	0.0	0.0–0.8 ‡	0.0	n/a	0.0	n/a	0.0	n/a	0.76 / n
HIV [−]			61,966	35,640	CIN2+	236	0.1	0–0.2	0.3	0.2–0.4	0.4	0.3–0.5	0.5	0.4–0.6	
					CIN3+	77	0.1	0.1–0.1	0.1	0.1–0.1	0.2	0.2–0.2	0.2	0.2–0.2	
WLWH	n/a		10	8	CIN2+	0									/
					CIN3+	0									/
HIV [−]			1152	44	CIN2+	6									/
					CIN3+	2									/
WLWH	Any	Pos	84	79	CIN2+	19	14.4	6.7–22.1	16.5	8.4–24.6	18.7	10.1–27.4	22.0	12.0–32.0	
					CIN3+ §	5	3.8	0.0–8.0	3.8	0.0–8.1	4.6	0.3–8.9	6.4	1.0–11.8	0.77 / 0.
HIV [−]			2615	2357	CIN2+	522	17.2	15.7–18.7	19.6	18.0–21.2	21.9	20.2–23.6	23.5	21.7–25.3	
					CIN3+	234	8.5	7.4–9.7	9.6	8.4–10.8	10.4	9.1–11.7	11.0	9.6–12.3	
WLWH		Neg *	522	394	CIN2+	3	0.4	0–1.0	0.4	0–1.0	0.6	0–1.1	0.6	0–1.1	
					CIN3+ §	2	0.3	0.0–0.8	0.3	0.0–0.8	0.3	0.0–0.8	0.4	0.0–1.0	0.50 / 0.
HIV [−]			64,713	36,981	CIN2+	383	0.2	0.1–0.2	0.4	0.4–0.5	0.6	0.5–0.7	0.8	0.7–0.8	
					CIN3+	133	0.1	0.1–0.2	0.2	0.1–0.2	0.3	0.2–0.3	0.3	0.3–0.3	

HIV Status	HPV Result	Cytology Result	N_{Total}	$N_{informative}$ **	End point	N_{Cases}	Immediate (Prevalent)		1-Year Cumulative Risk		3-Year Cumulative Risk		5-Year Cumulative Risk		P_{CIN2+} † / P
							Risk (%)	95%CI (%)	Risk (%)	95%CI (%)	Risk (%)	95%CI (%)	Risk (%)	95%CI (%)	/
WLWH		n/a	2	1	CIN2+	0									/
					CIN3+	0									/
HIV[−]			145	58	CIN2+	2									/
					CIN3+	1									/
WLWH	Pos	Pos	71	66	CIN2+	18	16.4	7.5–25.3	18.7	9.4–28.1	21.2	11.3–31.2	24.9	13.4–36.4	0.77 / 0.
					CIN3+‡	5	4.6	0.0–9.6	4.6	0.0–9.6	5.5	0.1–10.9	7.6	0.3–14.9	
HIV [−]			2,249	2,081	CIN2+	494	19.5	17.8–21.2	22.2	20.4–24.0	24.8	22.9–26.7	26.6	24.6–28.7	
					CIN3+	230	9.6	8.4–10.9	10.9	9.5–12.2	11.8	10.4–13.2	12.4	10.9–13.9	
WLWH		Neg*	52	45	CIN2+	2	2.5	0.0–6.9	2.6	0.0–6.5	2.8	0.0–7.2	3.0	0.0–7.4	0.02 / 0.
					CIN3+‡	2	2.2	0.0–6.5	2.2	0.0–6.5	2.6	0.0–7.0	3.4	0.0–8.7	
HIV [−]			2,097	1,625	CIN2+	169	2.3	0.6–3.9	4.7	3.6–5.7	6.9	5.8–8.1	8.5	7.2–9.9	
					CIN3+	67	0.8	0.0–1.9	1.9	1.2–2.6	2.7	2.0–3.5	3.3	2.4–4.2	
WLWH		n/a	0	0	CIN2+	0									/
					CIN3+	0									/
HIV [−]			9	6	CIN2+	2									/
					CIN3 +	1									/
WLWH	Neg	Pos	11	11	CIN2+	1	1.6	0.0–5.7	2.1	0.0–6.4	2.7	0.0–7.5	3.6	0.0–9.8	0.59 / n
					CIN3+	0	0.0	0.0–33.5≠	0.0	n/a	0.0	n/a	0.0	n/a	
HIV [−]			321	258	CIN2+	23	1.4	0.4–2.4	1.6	0.6–2.6	1.8	0.8–2.7	1.9	1.0–2.8	
					CIN3+	11	1.0	0.0–2.2	1.0	0.0–2.2	1.1	0.0–2.3	1.1	0.0–2.3	
WLWH		Neg*	462	343	CIN2+	1	0.2	0.0–0.7	0.2	0.0–0.7	0.3	0.0–0.7	0.3	0.0–0.8	0.44 / n
					CIN3+	0	0.0	0.0–0.8≠	0.0	n/a	0.0	n/a	0.0	n/a	
HIV [−]			61,509	35,330	CIN2+	213	0.1	0.1–0.2	0.3	0.2–0.3	0.4	0.4–0.5	0.5	0.4–0.6	
					CIN3+	66	0.1	0.0–0.1	0.1	0.1–0.2	0.2	0.1–0.2	0.2	0.1–0.2	
WLWH		n/a	2	1	CIN2+	0									/
					CIN3+	0									/
HIV [−]			136	52	CIN2+	0									/
					CIN3+	0									/
WLWH	n/a	Pos	2	2	CIN2+	0									/
					CIN3+	0									/
HIV [−]			45	2	CIN2+	0									/
					CIN3+	0									/
WLWH		Neg	8	6	CIN2+	0									/

HIV Status	HPV Result	Cytology Result	N_{Total}	$N_{informative}$ **	End point	N_{Cases}	Immediate (Prevalent)		1-Year Cumulative Risk		3-Year Cumulative Risk		5-Year Cumulative Risk		P_{CIN2+} † / P
							Risk (%)	95%CI (%)	Risk (%)	95%CI (%)	Risk (%)	95%CI (%)	Risk (%)	95%CI (%)	/
					CIN3+	0									/
HIV [−]			1107	26	CIN2+	1									/
					CIN3+	0									/
WLWH		n/a	0	0	CIN2+	0									/
					CIN3+	0									/
HIV [−]			15	2	CIN2+	0									/
					CIN3+	0									/

*Included atypical squamous cells of undetermined significance if the concurrent HPV test was negative.

†Differences in 5-year risk between WLWH and HIV[−] for CIN2+
Differences in 5-year risk between WLWH and HIV[−] for CIN3+

‡Poisson exact confidence interval

✱Modeled in HPV+ subset

§Marginal analysis instead of weighted average

**$N_{informative}$ refers to women who contributed to the risk estimations because they were diagnosed with CIN2+ or had a negative assessment in follow-up.