original reports abstract

Unique Genomic Landscape of High-Grade Neuroendocrine Cervical Carcinoma: Implications for Rethinking Current Treatment Paradigms

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PURPOSE High-grade neuroendocrine cervical cancer (HGNECC) is an uncommon malignancy with limited therapeutic options; treatment is patterned after the histologically similar small-cell lung cancer (SCLC). To better understand HGNECC biology, we report its genomic landscape.

PATIENTS AND METHODS Ninety-seven patients with HGNECC underwent comprehensive genomic profiling (182-315 genes). These results were subsequently compared with a cohort of 1,800 SCLCs.

RESULTS The median age of patients with HGNECC was 40.5 years; 83 patients (85.6%) harbored high-risk human papillomavirus (HPV). Overall, 294 genomic alterations (GAs) were identified (median, 2 GAs/sample; average, 3.0 GAs/sample, range, 0-25 GAs/sample) in 109 distinct genes. The most frequently altered genes were *PIK3CA* (19.6% of cohort), *MYC* (15.5%), *TP53* (15.5%), and *PTEN* (14.4%). *RB1* GAs occurred in 4% versus 32% of HPV-positive versus HPV-negative tumors ($P < .0001$). GAs in HGNECC involved the following pathways: PI3K/AKT/mTOR (41.2%); RAS/MEK (11.3%); homologous recombination (9.3%); and ERBB (7.2%). Two tumors (2.1%) had high tumor mutational burden (TMB; both with *MSH2* alterations); 16 (16.5%) had intermediate TMB. Seventy-one patients (73%) had ≥ 1 alteration that was theoretically druggable. Comparing HGNECC with SCLC, significant differences in TMB, microsatellite instability, HPV-positive status, and in *PIK3CA*, *MYC*, *PTEN, TP53*, *ARID1A*, and *RB1* alteration rates were found.

CONCLUSION This large cohort of patients with HGNECC demonstrated a genomic landscape distinct from SCLC, calling into question the biologic and therapeutic relevance of the histologic similarities between the entities. Furthermore, 73% of HGNECC tumors had potentially actionable alterations, suggesting novel treatment strategies for this aggressive malignancy.

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INTRODUCTION

The treatment of solid malignancies has evolved and is perhaps best exemplified by the approach to non–small-cell lung cancer, for which molecular characterization and use of targeted agents have emerged as standard therapeutic paradigms. Recently, The Cancer Genome Atlas (TCGA) completed and published the integrated genomic and molecular characterization of cervical cancer.[1] In addition to data previously released for both ovarian (high-grade serous) and endometrial (endometrioid and serous) cancers, this publication completed the molecular and genomic evaluation of the most common gynecologic malignancies.[2,3]

Traditionally, cervical cancer clinical trials have excluded less common histologies such as high-grade neuroendocrine cervical carcinoma (HGNECC). Despite the low incidence of HGNECC (< 2% of all cervical cancers) the oncologic impact is significant because these tumors exhibit more aggressive clinical characteristics.[4,5] Unfortunately, the 5-year overall survival rate for patients with early-stage disease is only a 36%, and those with metastatic spread face an even more dismal prognosis. Given these poor outcomes, patients with HGNECC represent an area of unmet clinical need.

Developing therapeutic options for patients with rare tumors is challenging, relying on international collaboration, as well as small case series or retrospective reports rather than prospective clinical trials. The current therapeutic paradigm for the treatment of HGNECC was adopted from the more common, morphologically similar, small-cell lung cancer (SCLC) and includes surgical resection if feasible, followed by platinum plus etoposide-based combination chemotherapy, and possibly radiation.[6,7] There are few studies informing treatment of recurrent disease, and there are no drugs

ASSOCIATED CONTENT

Appendix

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objective

To define the molecular landscape of high-grade neuroendocrine cervical cancer in a large cohort of patients.

Knowledge Generated

High-grade neuroendocrine cervical cancer appears molecularly distinct from the histologically similar small-cell lung cancer. Up to 73% of patients' samples harbored potentially actionable alterations, informing novel treatment strategies.

Relevance

Continued understanding of the molecular underpinnings of high-grade neuroendocrine cervical carcinoma will be critical to driving drug discovery for this disease.

approved by the Food and Drug Administration (FDA) specifically for HGNECC.[8]

Recently, 2 reports of exceptional responses to immune checkpoint inhibition in patients with recurrent HGNECC were published.[9,10] To better understand these responses and to identify molecular aberrations underlying this uncommon malignancy, we examined the genomic landscape of HGNECC. Here, we report the identified molecular alterations in a cohort of HGNECC specimens, several of which may serve as actionable therapeutic targets, and compare the genomic landscape of this disease to the histologically similar SCLC, which has been historically used to model treatment of HGNECC.

PATIENTS AND METHODS

We evaluated a fully informative genomic profile of patients diagnosed with poorly differentiated (G3) neuroendocrine cervical carcinomas inclusive of both small- or large-cell subtypes (HGNECCs) whose cancers were submitted for hybrid capture–based next-generation sequencing (NGS) testing from March 2013 to December 2017 (N = 97). A cohort of 1,800 similarly tested cases of SCLC from the same period were subsequently evaluated to allow for comparison of genomic alterations (GAs). The submitting physicians provided specification of a poorly differentiated, neuroendocrine tumor type of cervical origin, which was then independently reviewed by a gynecologic pathologist (J.E.) to confirm high-grade neuroendocrine pathologic features in the pathology report and/or the representative sample of tumor submitted for sequencing (grade 3 cytomorphologic features, some component of small-cell or large-cell carcinoma histology, and/or positivity for neuroendocrine markers). The database was de-identified with only the diagnosis available. NGS data were generated by FoundationOne (Foundation Medicine; Cambridge, MA). The study was performed in accordance with University of California, San Diego, Institutional Review Board guidelines for a de-identified database. Approval for this study, including a waiver of informed consent and a Health Insurance Portability and Accountability Act waiver of authorization, were also obtained from the Western Institutional Review Board (Protocol No. 20152817).

Tissue Samples and Mutational Analysis

Available tissue from diagnostic or therapeutic procedures was used to determine oncogenic molecular alterations. Sequencing information was collected on 97 patients with HGNECC and 1,800 with SCLC, whose formalin-fixed, paraffin-embedded tumor samples were submitted to Foundation Medicine for genomic profiling. The test sequences the entire coding region of 182 or, more recently, 236 or 315 cancer-related genes plus up to 47 introns of up to 19 genes often rearranged or altered in cancer to an average depth of coverage of $> 500\times$.[11] The pathologic diagnosis of each case was confirmed on routine hematoxylin- and eosin-stained slides and all samples forwarded for DNA extraction contained a minimum of 20% tumor nuclear area. Microsatellite instability (MSI) status was evaluable in 75 HGNECC and 1,573 SCLC cases.

The sequencing methods used for comprehensive genomic profiling have been validated and reported previously (Appendix).[12,13] The optimized loci used to evaluate MSI status were selected from a total set of 1,897 that have adequate coverage on all versions of the assay. Each locus is intronic and has a reference repeat length of 10-20 bp, which allows for analysis with the read length used by FoundationOne testing. Principal components analysis is used to produce an NGS-based MSI score. There was no need to extend beyond the first principal component, because it explained approximately 50% of the total data variance, whereas none of the other principal components explained $> 4\%$ each. Ranges of the MSI score were assigned MSI-High (MSI-H), MSI ambiguous, or microsatellite stable (MSS). MSI-Low calls are not made because there was no gold-standard test set, but we presume such samples would significantly overlap with the MSI-ambiguous category reported here. For samples in which MSI-specific quality control criteria were not met (n = 22 HGNECC; n = 227 SCLC), a status of MSI unknown was assigned,[14] and these cases were excluded from additional MSI analysis.

Tumor Mutational Burden

The number of somatic mutations detected on NGS (interrogating up to 1.2 Mb of the genome) were quantified

and that value extrapolated to the whole exome, using a validated algorithm.[15] Alterations likely or known to be germline polymorphisms or bona fide oncogenic drivers were excluded. Tumor mutational burden (TMB) was measured in mutations per megabase. TMB levels were grouped into 3 bins: TMB-low (TMB-L; 1-5 mutations/Mb), intermediate (TMB-I; 6-19 mutations/Mb), and high (TMB-H; ≥ 20 mutations/Mb). The cutoff of 20 coding mutations/Mb is approximately equal to 400 nonsynonymous mutations per exome.[15]

Human Papillomavirus Detection

In addition, the presence of high-risk human papillomavirus (HPV) was examined in submitted specimens, as previously reported.[16] Hybrid-capture reagents included baits designed to capture unique regions of select viral genomes including HPV-16 and -18. Sequence read pairs were aligned to the reference genome of the respective viral genomes, and the number of pairs mapping to each viral genome was counted. A total HPV-16/18 aligned read count of ≥ 5 reads per million was considered a positive HPV status, and < 5 reads per million was considered HPV not detected.[16]

End Points and Statistical Methods

Descriptive statistics were used to summarize the baseline patient characteristics. Fisher exact test was used to determine the association between categorical variables in univariate analysis and the Z-test was used to assess population differences, where appropriate. All tests were 2 sided. All statistical tests were carried out using GraphPad Prism, version 6.0 (GraphPad Software, San Diego, CA).

RESULTS

Characterization of GAs in HGNECC

The median age of the cohort was 40.5 years (range, 25-77 years). Of the 97 patients, 83 were high-risk HPV positive (85.6%) and 14 were negative (14.4%). All samples were reflective of HGNECC, including both small-cell and large-cell HGNECC cases. Among the HGNECC cohort (N = 97), the most frequently identified GAs (discerned in > 10% of the cohort) involved *PIK3CA* (19.6% of patients), *MYC* (15.5%), *TP53* (15.5%), and *PTEN* (14.4%) (Fig 1; a detailed list of all GAs can be found in Appendix Table A1).

A total of 109 different genes were mutated in the 97 patient samples evaluated (variants of unknown significance were excluded from all analyses). The most frequently reported number of GAs per sample was 2, with a range of 0-25 (average, 3.0 GAs/sample; Fig 2). When evaluating TMB, 2 cases (2.1%) were TMB-H and 16 cases (16.5%) were TMB-I. Most patients' tumors (n = 79; 81.4%) were TMB-L (Table 1). Nine patient samples had no known or likely GAs on comprehensive genomic profiling. Of the 88 patients who had an alteration, 72 had at least 1 alteration for which there currently existed an agent potentially targeting that alteration.

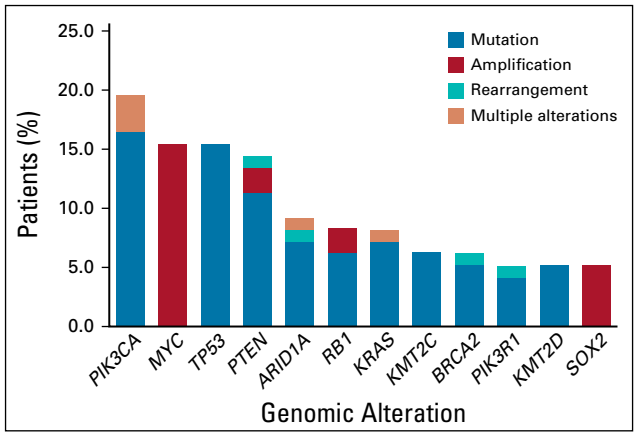

FIG 1. Most common genomic alterations in patients with high-grade neuroendocrine cervical cancer (HGNECC), reflected as percentage of patients (N = 97). Only genes altered in > 5% of samples are depicted. Variants of unknown significance excluded.

Genomics in HPV-Positive Versus -Negative Patients

When examining distribution of GAs on the basis of HPV detection status, a significant difference was identified in the frequency of several GAs, including *PIK3CA*, *TP53*, *PTEN*, *ARID1A*, and *RB1*, all of which were more frequent in the HPV-negative subgroup (Table 1). There was no difference in the frequency of TMB-H between HPV-positive and HPV-negative or unknown samples ($P = .2691$).

Mismatch Repair Gene Aberrations Associated With MSI-High

Three cases (3%) had pathogenic *MSH2* alterations. Two of the 3 cases were both MSI-H and TMB-H and harbored the highest numbers of identifiable GAs in the cohort.[17,18] The third case, with a nonsense mutation near the 3′ end of the coding sequence (MSH2 R929*), was MSS and TMB-L. The 2 MSH-2–mutant MSI-H cases were both of small-cell histology and accounted for all MSI-H cases out of the 75

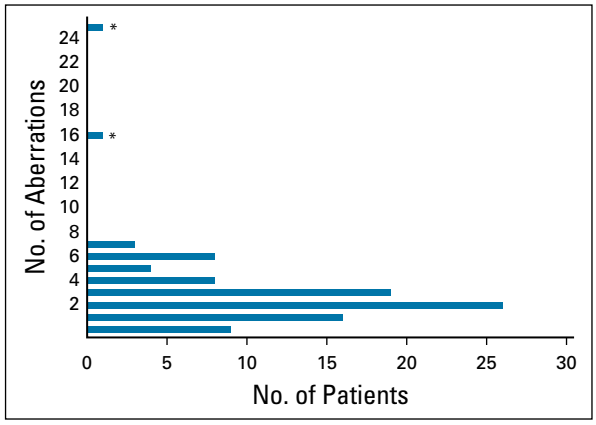

FIG 2. Number of reported genomic alterations per patient. Variants of unknown significance are excluded. (*) Tumor mutational burden high (*MSH2* mutation).

TABLE 1. Molecular Features of High-Grade Neuroendocrine Cervical Cancers

	Patients With ≥ 1 Oncogenic Alteration (N = 97)			
Altered Gene	**Total**	**HPV Positive (n = 83)**	**HPV Negative (n = 14)**	***P***
PIK3CA	19.6	17	36	.0037
MYC	15.5	17	7	.0484
TP53	15.5	11	43	.0001
PTEN	14.4	8	50	.0001
ARID1A	9.3	5	36	.0001
RB1	8.2	4	36	.0001

NOTE. The No. (%) of low (1-5 mutations/Mb), intermediate (6-19 mutations/Mb), and high (≥ 20 mutations/Mb) tumor mutational burdens were as follows: patients with ≥ 1 HPV-positive oncogenic alteration: 70 (84), 12 (14.4), and 1 (1.2), respectively; and for patients with ≥ 1 HPV-negative oncogenic alteration: 9 (64.3) 4 (28.6), and 1 (7.1), respectively (P = .13).

cases of HGNECC with evaluable microsatellite status (2.7%).

Less Frequent GAs

Additional genomic characterization was performed in which we specifically explored the homologous recombination deficiency (HRD), RAS, PI3K/AKT/mTOR, and ERBB pathways. Nine cases (9.3%) were had GAs in HRD-related genes, with the most frequent alterations noted in *BRCA2* (n = 6 of 9; 66.7%).[17,19] Three additional patient samples had *BRCA1*, *ATM*, and *PALB2* mutations (n = 1 in each case) case (n = 3 of 9; 33.3%).

Eleven patient samples (11.3%) had alterations in the RAS pathway, with *KRAS* and *BRAF* mutations being the most frequent (72.7% [n = 8 of 11] and 27.3% [n = 3 of 11], respectively). Of the identified BRAF mutations, only 1 was a V600E alteration. Furthermore, a total of 40 patient samples (41.2%) harbored mutations in the PI3K/AKT/mTOR pathway; mutations in *PIK3CA* were identified in 47.5% of these samples (n = 19), and *PTEN* mutations were reported in 35% (n = 14). Last, 7 patients (7.2%) had mutations in the ERBB pathway, with *ERBB2* mutations occurring in tumors of 4 individuals (57.1%).

Comparison of HGNECC and SCLC

Given the histologic similarity between SCLC and HGNECC, tumor samples from a cohort of 1,800 patients with SCLC were compared with the HGNECC samples (Table 2). The SCLC samples featured significantly lower frequencies of GAs in *PIK3CA*, *MYC*, and *ARID1A*. In contrast, the HGNECC samples featured significantly lower frequencies of GAs in *TP53* and *RB1*. High-risk HPV was identified in much less than 1% of SCLC tumor samples compared with 85.6% of HGNECC tumor samples. There was a single MSI-H SCLC case (n = 1 of 1,449; < 0.001%), whereas MSI-H status was found in 2 HGNECC cases (2.7%). Last, TMB was significantly higher in the SCLC samples compared with the HGNECC samples with respect to both intermediate and high TMB levels. The small-cell subset of HGNECC samples showed analogous gene mutation differences from SCLC.

DISCUSSION

Neuroendocrine carcinoma is an uncommon but aggressive variant accounting for approximately 1.5% of all newly diagnosed cervical cancers.[20] The great majority of these lesions are high-grade large- or small-cell subtypes, with only rare reports of well-differentiated cervical carcinoid tumors.[20] The treatment of patients with HGNECC remains

TABLE 2. Comparison of Clinical and Molecular Features of HGNECC, Cervical Small-Cell Carcinoma, and SCLC

Feature	**HGNECC (N = 97)**	**Cervical Small Cell (n = 79)[a]**	**SCLC (n = 1,800)**	**Cervical Small Cell *v* SCLC, *P***	**HGNECC *v* SCLC, *P***
Median age, years (range)	40.5 (25-77)	40.5 (24-73)	64 (10-89)	.001	.0001
Genomic alterations/case	3.0	3.0	4.6	NS	NS
PIK3CA	19.6	24.0	5.1	.0001	.0001
MYC	15.5	12.7	6.3	.0001	.0001
TP53	15.5	12.7	90.1	.0001	.0001
PTEN	14.4	13.9	8.9	NS	NS
ARID1A	9.3	10.1	4.2	.012	.01778
RB1	8.2	6.3	70.9	.0001	.0001
MSI-High[b]	2.7	3.1	0.004	.0001	.0001
TMB ≥ 6-19 mutations/Mb	16.5	15.2	62.3	.0001	.0001
TMB ≥ 20 mutations/Mb	2.1	2.5	8.2	.0767	.030
HPV-16/18 positive	85.6	87.0	0.01	.0001	.0001

NOTE. Data reported as % unless otherwise indicated.

Abbreviations: HGNECC, high-grade neuroendocrine cervical cancer; HPV, human papillomavirus; MSI, microsatellite instability; NS, not significant; SCLC, small-cell lung cancer; TMB, tumor mutational burden.

[a]The 79 patients with cervical small-cell cancers were a subset of the 97 patients with HGNECC.

[b]MSI status was evaluated in 75 HGNECC cases, 64 cervical small-cell cases, and 1,449 SCLC cases.

clinically challenging, with limited response rates to chemotherapy; however, anecdotal reports of exceptional responders have been described.[9,10]

The paradigm for management of HGNECC has been informed by the treatment of the more commonly diagnosed (and histologically similar) SCLC, which accounts for approximately 15% of all lung cancer cases. In prior studies, whole-genome sequencing of 110 SCLC specimens identified essentially ubiquitous *TP53* and *RB1* inactivating mutations, with biallelic losses of each gene respectively in 100% and 93% of cases without chromothripsis.[21]

In an effort to better define the molecular landscape of HGNECC, we evaluated the comprehensive genomic profiling of 97 patient samples. The most frequently identified GA was *PIK3CA* mutation, occurring in 19.6% of submitted samples (n = 19). At least 1 characterized alteration was identified in 88 patient samples (90.7%) and of these, 72 had a potentially pharmacologically tractable alteration.

Interestingly, the frequency and distribution of GAs identified in this cohort of patients are similar and distinct from mutational patterns described in the more common HPV-related cervical cancer histologies.[1] As detailed in TCGA's integrated genomic characterization of cervical cancer (ie, squamous, adenocarcinoma, and adenosquamous histologies), mutations in the *PIK3CA* gene were the most frequently identified aberration, occurring in 26% of samples, approximating the nearly 20% rate in our cohort. In addition, significantly mutated genes reported by the TCGA, identified in similar proportions in this patient cohort, included *ARID1A* (7% in TCGA and 9.3% in our cohort) and *KRAS* (6% in TCGA and 8.2% in our cohort). Conversely, the examined neuroendocrine cohort had a greater frequency of *PTEN* mutations (8% in TCGA *v* 14.4% in our cohort). These molecular differences may be reflective of the varying histologies or, potentially, the differential high-risk HPV detection rates (85.6% in our cohort *v* 95% in the TCGA).[1] Importantly, the high-risk HPV rate in our cohort should be interpreted with caution because the assay used has not undergone formal concordance study with gold standard tests such as hybrid capture and can detect only HPV 16/18.

Our own, much larger cohort of SCLC samples (n = 1,800) recapitulates prior studies and had a strikingly different molecular portfolio when compared with HGNECC samples. The frequency of *TP53* and *RB1* alterations in the SCLC cohort significantly exceeded that seen in our HGNECC cohort (15.5% and 8.2%, respectively), the HPV16/18 positive subset (11% and 4%, respectively), and the subset where HPV16/18 was not detected (43% and 36%, respectively; Table 2). Furthermore, mutations affecting the *NOTCH* pathway were identified in 25% of the examined SCLC samples; the *NOTCH* pathway is hypothesized to function as a regulator of neuroendocrine differentiation. In our examined HGNECC cohort, only 7 patients (7.2%) had *NOTCH* alterations. Alterations in *PIK3CA*, *MYC*, and *PTEN* were significantly more common in HGNECC when compared with SCLC (Table 2). MSI-H status was also more common in the HGNECC cohort whereas TMB-I/TMB-H was more common in SCLC (despite the lack of MSI-H status). Finally, HPV positivity was discerned in 85.6% of our HGNECC samples, but in only 0.01% of our SCLC samples ($P < .0001$). No parallels in molecular alterations were identified when comparing our findings for HGNECC with those of prior SCLC studies, supporting our premise that the similarity between these entities is largely morphologic and the treatment approaches for HGNECC can likely be improved through improved molecular granularity.

Despite the infrequency of HGNECC, the identification of potentially actionable GAs may inform treatment of a subset of patients with historically limited therapeutic options.[18,22-25] In this cohort of patients, aberrations in the PI3K/AKT/mTOR pathway were commonly seen (*PIK3CA* [19.6%]; *PTEN* [14.4%]). The use of everolimus, or an alternate mTOR or PIK3CA inhibitor, may be considered in such circumstances, although the utility of a PIK3CA mutation in predicting response to single-agent everolimus in the presence of multiple GAs remains limited.[26,27]

Although less frequently identified, alterations in the HRD pathway were detected in 9.3% of patient samples, potentially supporting use of a poly-ADP ribose polymerase inhibitor. The identification of both TMB-H (n = 2) and GAs in mismatch repair genes (n = 3) may also inform the use of immune checkpoint inhibition.[28] In May 2017, the FDA approved pembrolizumab for the treatment of mismatch repair–deficient or MSI-H solid tumors that progressed after prior therapy. This disease site–agnostic approval allows for a promising therapeutic option for patients with a previously unmet clinical need. More recently, the FDA accepted and granted priority review to a supplemental Biologics License Application for pembrolizumab for the treatment of adult and pediatric patients with unresectable or metastatic solid tumors with tissue TMB-H whose disease has progressed after prior treatment and who have no satisfactory alternative treatment options, supported by data from the phase II Keynote-158 trial. Notably, there are 2 published case reports of patients with recurrent, treatment-refractory HGNECC with exceptional and durable responses to checkpoint inhibition; 1 of these tumors was from our current HGNECC cohort and had a mismatch repair defect and the other lacked correlative genomic testing.[9,10]

Last, the identification of *ARID1A* (9.3%) and *SMARCA4* (4.1%) mutations may predict sensitivity to an alternate therapeutic strategy.[29] Homeostasis requires balanced *ARID1A* and *EZH2* activity, facilitated via chromatin-mediated gene expression. Loss of *ARID1A* expression results in imbalanced EZH2 activity, and use of an EZH2 inhibitor such as tazemetostat may capitalize on this oncogene addiction. Importantly, 2 of the 4 SMARCA4

aberrations were identified in patients with MSI-H lesions, possibly reflecting that the SMARCA4 may be a passenger mutation resulting from the underlying MSI. Furthermore, of the 4 cases with SMARCA4 alterations, 1 was HPV-18 positive and another was p16 positive by immunohistochemical assessment.

Despite the large sample size and robust genomic data, this study has limitations. The retrospective design and use of archival tumor tissues from various time points during therapy may make interpretation of GAs difficult. In addition, the lack of demographic and clinical data, as well as treatment history, precludes exploratory assessments of response to a selected targeted agent. Last, HPV status was determined using molecular surrogates that differ from the assays used in clinical practice. It remains unclear if HPV infection is a prerequisite for neuroendocrine cervical carcinoma, although recent publications suggest > 85% of neuroendocrine cervical carcinomas are HPV positive, with HPV-16 and HPV-18 accounting for > 95% of the identified high-risk HPV strains.[30]

This report highlights the potential therapeutic utility of genomic testing in patients with this uncommon disease.[27] Of interest, despite the histologic similarity between HGNECC and SCLC, which has led to the latter being used as a model for treating the former, the molecular portfolio of these 2 entities is strikingly different. Therefore, it is plausible that patients with HGNECC may benefit from alternative therapeutic strategies.

It is not anticipated that traditional prospective trials will accrue sufficient patient numbers in this disease setting, and novel study designs, including umbrella, basket, and platform trials, should be considered given the presence of actionable targets. Interestingly, the first reported cohort of the DART trial (ClinicalTrials.gov identifier: NCT02834013)[31] was the neuroendocrine cohort, with a 44% overall response rate in those with high-grade disease. Ultimately, comprehensive genomic characterization may catalyze the investigation and identification of effective therapies, allowing us to improve oncologic outcomes in this aggressive disease.

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APPENDIX

Sequencing Methods Used for Comprehensive Genomic Profiling

Sample processing and sequencing were performed in a Clinical Laboratory Improvement Amendments– and College of American Pathologists–accredited laboratory. Briefly, after pathologic review to confirm sufficient tumor nuclei (minimum, 20%) and mitigate pathologic inconsistencies, at least 50 ng of DNA was extracted from 40 microns of tumor samples provided as formalin-fixed, paraffin-embedded tissue blocks. The samples were assayed using adaptor-ligation and hybrid-capture next-generation sequencing (FoundationOne) for all coding exons from 182 (version 1), 287 (version 2), or 315 (version 3) cancer-related genes plus selected introns from 14 (version 1), 19 (version 2), or 28 (version 3) genes frequently rearranged in cancer.

Sequencing of captured libraries was performed using HiSEquation 2500/4000 (Illumina, San Diego, CA) to a mean exon coverage depth of $>$ 500×, and resultant sequences were analyzed using both an algorithmic pipeline and manual curation for base substitutions, small insertions or deletions (indels), copy number alterations (focal amplifications and homozygous deletions), and selected gene fusions, as previously described.[13] Clinically relevant genomic alterations were defined as alterations targetable by anticancer drugs currently available on the market or in registered clinical trials. Germline variants documented in the dbSNP database (dbSNP142; http://www.ncbi.nlm.nih.gov/SNP/), with $\geq$ 2 counts in the ExAC database (http://exac.broadinstitute.org/), or recurrent variants of unknown significance that were predicted by an internally developed algorithm to be germline were removed, with the exception of known driver germline events.[12] Known, confirmed somatic alterations deposited in the Catalog of Somatic Mutations in Cancer (version 62) were highlighted as biologically significant, as were inactivating events in tumor suppressor genes. To maximize mutation-detection accuracy (sensitivity and specificity) in impure clinical specimens, the test was previously optimized and validated to detect base substitutions at a $\geq$ 5% mutant allele frequency (MAF), indels with a $\geq$ 10% MAF with $\geq$ 99% accuracy, and fusions occurring within baited introns/exons with $>$ 99% sensitivity.[12] Each tumor sample was analyzed alongside an internally validated mixture of 10 heterozygous diploid HapMap control samples, which custom algorithms used to normalize the sequence coverage distribution across baited targets.

TABLE A1. Detailed Genomic Assessment of High Grade Neuroendocrine Cervical Cancer Samples

Case No.	No. of Genes Assessed	Gene	Age (years)	Functional Status	Alteration Type	Description
HGNECC_1	236	*AKT3*	42	Known	CN	Amplification
HGNECC_1	236	*KDM6A*	42	Known	SV	V607M
HGNECC_1	236	*MCL1*	42	Known	CN	Amplification
HGNECC_10	236	*ALK*	40	Known	SV	L560F
HGNECC_11	315	*FGFR2*	44	Known	SV	S252W
HGNECC_11	315	*MED12*	44	Known	SV	D23Y
HGNECC_11	315	*PTEN*	44	Known	SV	R130P
HGNECC_11	315	*RB1*	44	Known	SV	G442fs*15
HGNECC_11	315	*TP53*	44	Known	SV	R175H
HGNECC_12	315	*ARID1A - N/A*	66	Likely	RE	Truncation
HGNECC_12	315	*TET2*	66	Known	SV	R1516*
HGNECC_13	315	*LRP1B - LRP1B*	58	Likely	RE	Deletion
HGNECC_13	315	*PTEN*	58	Known	SV	T319fs*1
HGNECC_14	315	*ARID1A*	59	Likely	SV	N104fs*6
HGNECC_14	315	*ERBB2*	59	Known	CN	Amplification
HGNECC_14	315	*PIK3CA*	59	Known	SV	E545A
HGNECC_14	315	*RB1*	59	Known	SV	R255*
HGNECC_14	315	*TOP2A*	59	Known	CN	Amplification
HGNECC_14	315	*TP53*	59	Known	SV	R158L
HGNECC_15	315	*BRCA1*	58	Likely	SV	Q780*
HGNECC_15	315	*IGF1*	58	Known	CN	Amplification
HGNECC_15	315	*MYC*	58	Known	CN	Amplification
HGNECC_15	315	*NOTCH2*	58	Known	SV	P6fs*27
HGNECC_15	315	*TP53*	58	Likely	SV	L330fs*15
HGNECC_16	236	*TP53*	46	Known	SV	D281N
HGNECC_17	315	*BRAF*	40	Known	SV	V600E
HGNECC_17	315	*CDK12*	40	Known	SV	G909R
HGNECC_17	315	*GRIN2A*	40	Known	SV	R1318W
HGNECC_18	315	*MED12*	34	Known	SV	G44A
HGNECC_19	315	*CDH1*	45	Known	SV	W20*
HGNECC_19	315	*NFE2L2*	45	Known	SV	D29H
HGNECC_19	315	*NFE2L2*	45	Known	SV	R34Q
HGNECC_19	315	*PIK3CA*	45	Known	SV	E545K
HGNECC_2	236	*IRS2*	35	Known	CN	Amplification
HGNECC_2	236	*MYCN*	35	Known	CN	Amplification
HGNECC_20	315	*MYC*	33	Known	CN	Amplification
HGNECC_21	182	*MYC*	27	Known	CN	Amplification
HGNECC_21	182	*TP53*	27	Known	SV	R273C
HGNECC_22	236	*MLL2*	55	Known	SV	R1702*
HGNECC_22	236	*TP53*	55	Known	SV	R280T
HGNECC_23	236	*BRCA2*	61	Known	SV	I2627F
HGNECC_23	236	*PIK3R1 - PIK3R1*	61	Likely	RE	Truncation
HGNECC_23	236	*PPP2R1A*	61	Known	SV	P179R
HGNECC_23	236	*PTEN*	61	Known	CN	Deletion

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TABLE A1. Detailed Genomic Assessment of High Grade Neuroendocrine Cervical Cancer Samples (Continued)

Case No.	No. of Genes Assessed	Gene	Age (years)	Functional Status	Alteration Type	Description
HGNECC_23	236	*RB1*	61	Known	CN	Deletion
HGNECC_23	236	*TP53*	61	Known	SV	R248Q
HGNECC_24	236	*ARID1A*	38	Likely	SV	A141fs*42
HGNECC_24	236	*ARID1A*	38	Likely	SV	Q1397fs*46
HGNECC_24	236	*CTNNB1*	38	Known	SV	S37C
HGNECC_24	236	*PIK3CA*	38	Known	SV	H1047R
HGNECC_24	236	*PTEN*	38	Known	SV	D92E
HGNECC_24	236	*PTEN*	38	Known	SV	Y180*
HGNECC_25	315	*MYC*	25	Known	CN	Amplification
HGNECC_26	315	*KRAS*	25	Known	SV	G13D
HGNECC_26	315	*MYC*	25	Known	CN	Amplification
HGNECC_27	315	*ABL2*	49	Known	SV	P497fs*7
HGNECC_27	315	*ATRX*	49	Likely	SV	D1940fs*15
HGNECC_27	315	*BLM*	49	Known	SV	N515fs*16
HGNECC_27	315	*ERBB3*	49	Known	SV	R475W
HGNECC_27	315	*FBXW7*	49	Known	SV	R465H
HGNECC_27	315	*FGF6*	49	Known	SV	V127M
HGNECC_27	315	*JAK1*	49	Known	SV	K860fs*16
HGNECC_27	315	*JAK1*	49	Known	SV	P430fs*2
HGNECC_27	315	*MEN1*	49	Likely	SV	R521fs*43
HGNECC_27	315	*MLL2*	49	Likely	SV	P2302fs*20
HGNECC_27	315	*MLL3*	49	Known	SV	K2797fs*26
HGNECC_27	315	*MSH2*	49	Likely	SV	E48*
HGNECC_27	315	*MSH2*	49	Likely	SV	Q324*
HGNECC_27	315	*NOTCH1*	49	Known	SV	R1586H
HGNECC_27	315	*PIK3CA*	49	Known	SV	E545D
HGNECC_27	315	*PREX2*	49	Known	SV	S565fs*3
HGNECC_27	315	*PTEN*	49	Known	SV	K267fs*9
HGNECC_27	315	*PTEN*	49	Known	SV	R130Q
HGNECC_27	315	*QKI*	49	Known	SV	A338T
HGNECC_27	315	*SETD2*	49	Likely	SV	F636fs*6
HGNECC_27	315	*SMARCA4*	49	Likely	SV	Q214*
HGNECC_27	315	*SMARCA4*	49	Likely	SV	T296fs*7
HGNECC_27	315	*STK11*	49	Likely	SV	W332*
HGNECC_27	315	*TET2*	49	Known	SV	R550*
HGNECC_27	315	*TET2*	49	Likely	SV	R1440fs*38
HGNECC_28	315	*MLL2*	60	Likely	SV	L951fs*7
HGNECC_28	315	*PTCH1*	60	Known	SV	R682C
HGNECC_28	315	*PTEN - ANKRD22*	60	Likely	RE	truncation
HGNECC_29	315	*CREBBP*	38	Likely	SV	S2377*
HGNECC_29	315	*KRAS*	38	Known	CN	Amplification
HGNECC_29	315	*KRAS*	38	Known	SV	G12D
HGNECC_3	315	*ARFRP1*	29	Known	CN	Amplification
HGNECC_3	315	*AURKA*	29	Known	CN	Amplification

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TABLE A1. Detailed Genomic Assessment of High Grade Neuroendocrine Cervical Cancer Samples (Continued)

Case No.	No. of Genes Assessed	Gene	Age (years)	Functional Status	Alteration Type	Description
HGNECC_3	315	*GNAS*	29	Known	CN	Amplification
HGNECC_30	315	*PTEN*	24	Likely	SV	M205fs*14
HGNECC_32	315	*BRD4*	67	Likely	SV	F656fs*4
HGNECC_32	315	*ERBB3*	67	Known	SV	V104L
HGNECC_32	315	*FBXW7*	67	Known	SV	R505C
HGNECC_32	315	*KRAS*	67	Known	SV	G12V
HGNECC_33	315	*MLL3*	42	Known	SV	R380C
HGNECC_33	315	*PIK3CA*	42	Known	CN	Amplification
HGNECC_33	315	*PIK3CA*	42	Known	SV	E545K
HGNECC_33	315	*SOX2*	42	Known	CN	Amplification
HGNECC_34	315	*ARID1A*	52	Likely	SV	D1850fs*33
HGNECC_34	315	*CIC*	52	Known	SV	D473N
HGNECC_34	315	*CTCF*	52	Likely	SV	T204fs*26
HGNECC_34	315	*GRM3*	52	Known	SV	G621V
HGNECC_34	315	*MSH2*	52	Likely	SV	C199fs*15
HGNECC_34	315	*MSH2*	52	Likely	SV	Q846*
HGNECC_34	315	*PIK3CA*	52	Known	SV	Q546H
HGNECC_34	315	*PIK3CA*	52	Known	SV	R38H
HGNECC_34	315	*PTEN*	52	Known	SV	N323fs*2
HGNECC_34	315	*PTPN11*	52	Known	SV	T468M
HGNECC_34	315	*RANBP2*	52	Known	SV	L811R
HGNECC_34	315	*RBM10*	52	Likely	SV	R98*
HGNECC_34	315	*RNF43*	52	Likely	SV	G659fs*41
HGNECC_34	315	*SMARCA4*	52	Likely	SV	L1161fs*3
HGNECC_34	315	*SMARCA4*	52	Likely	SV	P305fs*21
HGNECC_34	315	*SPEN*	52	Known	SV	R75H
HGNECC_35	315	*PPP2R1A*	77	Known	SV	P179R
HGNECC_35	315	*PTEN*	77	Known	SV	D92E
HGNECC_35	315	*PTEN*	77	Known	SV	L325R
HGNECC_35	315	*RB1*	77	Likely	SV	G89*
HGNECC_35	315	*SMARCA4*	77	Known	CN	Deletion
HGNECC_35	315	*TP53*	77	Known	SV	R306*
HGNECC_37	315	*FGF14*	50	Known	CN	Amplification
HGNECC_37	315	*IRS2*	50	Known	CN	Amplification
HGNECC_37	315	*KRAS*	50	Known	SV	K182_T183del
HGNECC_37	315	*PBRM1*	50	Likely	SV	Q1346*
HGNECC_38	315	*MSH2*	49	Likely	SV	R929*
HGNECC_38	315	*MYC*	49	Known	CN	Amplification
HGNECC_38	315	*PIK3R1*	49	Known	SV	T576del
HGNECC_38	315	*PTEN*	49	Known	SV	A126T
HGNECC_38	315	*RB1*	49	Known	CN	Deletion
HGNECC_38	315	*TP53*	49	Known	SV	K321fs*24
HGNECC_4	315	*EP300*	26	Likely	SV	A1437fs*65
HGNECC_4	315	*GNAS*	26	Known	SV	R201H

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TABLE A1. Detailed Genomic Assessment of High Grade Neuroendocrine Cervical Cancer Samples (Continued)

Case No.	No. of Genes Assessed	Gene	Age (years)	Functional Status	Alteration Type	Description
HGNECC_4	315	*MYC*	26	Known	CN	Amplification
HGNECC_4	315	*PTPRD*	26	Likely	SV	N1023fs*7
HGNECC_40	315	*AKT1*	35	Known	SV	W80R
HGNECC_40	315	*ARID1A*	35	Known	SV	R1276*
HGNECC_40	315	*ARID1B*	35	Likely	SV	Q1331*
HGNECC_40	315	*BRAF*	35	Known	SV	I326V
HGNECC_40	315	*CTNNB1*	35	Known	SV	D32Y
HGNECC_40	315	*PIK3CA*	35	Known	SV	C420_P421del
HGNECC_40	315	*PIK3R1*	35	Likely	SV	Splice site 1746-2A>G
HGNECC_41	236	*JAK2*	26	Known	CN	Amplification
HGNECC_42	236	*ARFRP1*	36	Known	CN	Amplification
HGNECC_42	236	*ERBB2*	36	Known	SV	S310F
HGNECC_42	236	*SRC*	36	Known	CN	Amplification
HGNECC_42	236	*TOP1*	36	Known	CN	Amplification
HGNECC_42	236	*TP53*	36	Known	SV	R248Q
HGNECC_42	236	*ZNF217*	36	Known	CN	Amplification
HGNECC_44	315	*FANCC - N/A*	72	Likely	RE	Truncation
HGNECC_44	315	*KRAS*	72	Known	SV	G12D
HGNECC_44	315	*NOTCH1*	72	Likely	SV	A305fs*27
HGNECC_44	315	*NOTCH1*	72	Likely	SV	Splice site 2354-1G>A
HGNECC_44	315	*PIK3CA*	72	Known	SV	R88Q
HGNECC_44	315	*RICTOR*	72	Known	CN	Amplification
HGNECC_45	315	*ARID2*	33	Likely	SV	S1157*
HGNECC_45	315	*CCNE1*	33	Known	CN	Amplification
HGNECC_45	315	*EPHA5*	33	Known	SV	S964Y
HGNECC_46	315	*CCNE1*	41	Known	CN	Amplification
HGNECC_46	315	*GRIN2A*	41	Known	SV	R19C
HGNECC_46	315	*NCOR1*	41	Likely	SV	Y1617*
HGNECC_47	315	*BCL2*	51	Known	CN	Amplification
HGNECC_47	315	*GATA6*	51	Known	CN	Amplification
HGNECC_47	315	*NKX2-1*	51	Known	CN	Amplification
HGNECC_49	315	*ARID1A*	59	Likely	SV	Splice site 4923_4993+259del330
HGNECC_49	315	*ARID1A - ARID1A*	59	Likely	RE	Deletion
HGNECC_49	315	*PALB2*	59	Likely	SV	Q141fs*27
HGNECC_5	315	*RB1*	40	Likely	SV	E629fs*12
HGNECC_50	315	*KRAS*	46	Known	SV	G13D
HGNECC_50	315	*MAGI2*	46	Known	SV	R564Q
HGNECC_51	315	*BRCA2 - N/A*	38	Likely	RE	Truncation
HGNECC_52	315	*NOTCH2*	73	Likely	SV	S1270fs*11
HGNECC_52	315	*PIK3R1*	73	Likely	SV	D330fs*15
HGNECC_53	315	*AKT1*	54	Known	SV	E17K
HGNECC_53	315	*ARID1A*	54	Likely	SV	Y1260fs*9
HGNECC_53	315	*BRCA2*	54	Likely	SV	N3124I
HGNECC_53	315	*GNAS*	54	Known	SV	R201C

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TABLE A1. Detailed Genomic Assessment of High Grade Neuroendocrine Cervical Cancer Samples (Continued)

Case No.	No. of Genes Assessed	Gene	Age (years)	Functional Status	Alteration Type	Description
HGNECC_53	315	*PIK3CA*	54	Known	SV	E542K
HGNECC_53	315	*RUNX1T1*	54	Known	SV	R395W
HGNECC_54	315	*PIK3CA*	34	Known	CN	Amplification
HGNECC_54	315	*PIK3CA*	34	Known	SV	E545K
HGNECC_54	315	*SOX2*	34	Known	CN	Amplification
HGNECC_55	315	*EP300*	34	Known	SV	D1399N
HGNECC_55	315	*MYCL1*	34	Known	CN	Amplification
HGNECC_55	315	*SOX2*	34	Known	CN	Amplification
HGNECC_56	315	*BRCA2*	45	Likely	SV	E1571fs*3
HGNECC_56	315	*MYC*	45	Known	CN	Amplification
HGNECC_56	315	*NCOR1*	45	Known	SV	R1794Q
HGNECC_56	315	*PIK3CA*	45	Known	SV	C420R
HGNECC_56	315	*PTEN*	45	Likely	SV	E307fs*1
HGNECC_56	315	*RB1*	45	Likely	SV	S397*
HGNECC_56	315	*TP53*	45	Known	SV	R248W
HGNECC_57	315	*FLT4*	28	Known	CN	Amplification
HGNECC_57	315	*KRAS*	28	Known	SV	G13C
HGNECC_57	315	*MLL3*	28	Likely	SV	Q419*
HGNECC_57	315	*NUP93*	28	Known	SV	E14K
HGNECC_58	315	*MYC*	30	Known	CN	Amplification
HGNECC_58	315	*SMARCA4*	30	Likely	SV	Y820*
HGNECC_59	315	*CIC*	35	Likely	SV	Q427*
HGNECC_59	315	*MYC*	35	Known	CN	Amplification
HGNECC_6	315	*CRLF2 - DHRSX*	44	Likely	RE	Fusion
HGNECC_6	315	*IRS2*	44	Known	CN	Amplification
HGNECC_60	315	*NUP93*	27	Known	SV	E14K
HGNECC_61	315	*MYC*	36	Known	CN	Amplification
HGNECC_61	315	*NOTCH2*	36	Known	SV	P6fs*27
HGNECC_61	315	*NOTCH4 - NOTCH4*	36	Likely	RE	Deletion
HGNECC_63	315	*BRCA2*	38	Known	SV	F1192C
HGNECC_63	315	*MYC*	38	Known	CN	Amplification
HGNECC_65	315	*ARID1A*	50	Likely	SV	E1060*
HGNECC_65	315	*CTNNB1*	50	Known	SV	S33C
HGNECC_65	315	*MLL2*	50	Likely	SV	Y1514fs*2
HGNECC_65	315	*PIK3CA*	50	Known	SV	V344G
HGNECC_65	315	*PTEN*	50	Known	SV	N184fs*6
HGNECC_65	315	*PTEN*	50	Likely	SV	E285*
HGNECC_66	315	*CCND2*	39	Known	CN	Amplification
HGNECC_66	315	*FGF23*	39	Known	CN	Amplification
HGNECC_66	315	*FGF6*	39	Known	CN	Amplification
HGNECC_66	315	*KDM5A*	39	Known	CN	Amplification
HGNECC_66	315	*KRAS*	39	Known	SV	G12S
HGNECC_66	315	*LRP1B*	39	Likely	SV	M1882fs*22
HGNECC_66	315	*MYC*	39	Known	CN	Amplification

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TABLE A1. Detailed Genomic Assessment of High Grade Neuroendocrine Cervical Cancer Samples (Continued)

Case No.	No. of Genes Assessed	Gene	Age (years)	Functional Status	Alteration Type	Description
HGNECC_67	315	*BRAF - N/A*	27	Likely	RE	Rearrangement
HGNECC_68	315	*EGFR*	60	Likely	SV	T415M
HGNECC_69	315	*BRD4*	49	Likely	SV	E1249*
HGNECC_69	315	*PIK3CA*	49	Known	SV	R88Q
HGNECC_69	315	*PIK3R2 - PIK3R2*	49	Likely	RE	Deletion
HGNECC_7	315	*MYCN*	47	Known	CN	Amplification
HGNECC_71	315	*FGF10*	43	Known	CN	Amplification
HGNECC_71	315	*NOTCH1*	43	Known	SV	V1575L
HGNECC_72	236	*PTEN*	35	Known	CN	Deletion
HGNECC_72	236	*TP53*	35	Known	SV	Splice site 375G>A
HGNECC_73	315	*MYC*	28	Known	CN	Amplification
HGNECC_73	315	*TP53*	28	Known	SV	R283C
HGNECC_74	315	*ERBB2*	65	Known	CN	Amplification
HGNECC_74	315	*IGF2R*	65	Known	SV	R1325H
HGNECC_74	315	*PTEN*	65	Known	SV	R130G
HGNECC_74	315	*PTEN*	65	Likely	SV	C250fs*4
HGNECC_74	315	*TP53*	65	Likely	SV	Splice site 783-1G>T
HGNECC_76	315	*ATRX*	35	Likely	SV	R1504*
HGNECC_78	315	*NUP93*	52	Known	SV	E14K
HGNECC_78	315	*SOX2*	52	Known	CN	Amplification
HGNECC_79	315	*MTOR*	38	Known	SV	T1834_T1837del
HGNECC_8	236	*LRP1B*	37	Known	SV	D3472N
HGNECC_8	236	*MCL1*	37	Known	CN	Amplification
HGNECC_80	315	*ATM*	28	Likely	SV	K468fs*18
HGNECC_80	315	*BRD4 - KIAA0319*	28	Likely	RE	Fusion
HGNECC_80	315	*MLL3*	28	Likely	SV	Y306*
HGNECC_82	236	*ARID1A*	48	Likely	SV	G1848fs*6
HGNECC_82	236	*CTNNB1*	48	Known	SV	G34V
HGNECC_82	236	*PIK3CA*	48	Known	SV	H1047R
HGNECC_83	315	*CCNE1*	37	Known	CN	Amplification
HGNECC_83	315	*IGF1R*	37	Known	CN	Amplification
HGNECC_83	315	*MYCN*	37	Known	CN	Amplification
HGNECC_84	236	*MCL1*	40	Known	CN	Amplification
HGNECC_84	236	*PIK3CA*	40	Known	SV	E545K
HGNECC_85	315	*AKT1*	45	Known	CN	Amplification
HGNECC_85	315	*CDKN1B - N/A*	45	Likely	RE	Rearrangement
HGNECC_86	315	*ERBB2*	52	Known	SV	S310Y
HGNECC_86	315	*RB1*	52	Likely	SV	Splice site 2490-1G>A
HGNECC_87	315	*MLL3*	38	Likely	SV	Y1348*
HGNECC_87	315	*PIK3CA*	38	Known	CN	Amplification
HGNECC_87	315	*PIK3CA*	38	Known	SV	E542K
HGNECC_87	315	*SOX9*	38	Likely	SV	Y503*
HGNECC_88	315	*BRCA2*	54	Likely	SV	E1608*
HGNECC_88	315	*MAGI2*	54	Known	SV	R1220*

(Continued on following page)

TABLE A1. Detailed Genomic Assessment of High Grade Neuroendocrine Cervical Cancer Samples (Continued)

Case No.	No. of Genes Assessed	Gene	Age (years)	Functional Status	Alteration Type	Description
HGNECC_89	315	*FGF10*	29	Known	CN	Amplification
HGNECC_89	315	*RICTOR*	29	Known	CN	Amplification
HGNECC_9	236	*FGF10*	27	Known	CN	Amplification
HGNECC_9	236	*MYC*	27	Known	CN	Amplification
HGNECC_9	236	*RICTOR*	27	Known	CN	Amplification
HGNECC_90	315	*DNMT3A*	73	Known	SV	R882H
HGNECC_90	315	*MLL2*	73	Likely	SV	Q5446*
HGNECC_90	315	*SOX2*	73	Known	CN	Amplification
HGNECC_91	315	*PIK3R1*	59	Known	SV	D560Y
HGNECC_92	315	*CDKN1B*	48	Likely	SV	P137fs*8
HGNECC_92	315	*GNAS*	48	Known	SV	R201H
HGNECC_92	315	*KIT*	48	Known	SV	D816V
HGNECC_92	315	*TP53*	48	Known	SV	R248Q
HGNECC_93	315	*DDR2*	46	Known	SV	T836M
HGNECC_93	315	*MUTYH*	46	Known	SV	G382D
HGNECC_94	315	*MERTK*	35	Known	SV	R865Q
HGNECC_94	315	*PIK3CA*	35	Known	SV	N345K
HGNECC_95	315	*MUTYH*	58	Known	SV	Y165C
HGNECC_95	315	*PIK3CA*	58	Known	SV	E726K
HGNECC_96	315	*CDKN1B*	67	Likely	SV	S27*
HGNECC_96	315	*CUL4B*	67	Known	SV	S110F
HGNECC_96	315	*PIK3CA*	67	Known	SV	D350G
HGNECC_96	315	*TP53BP1*	67	Known	SV	E1165K
HGNECC_97	315	*FGF10*	63	Known	CN	Amplification
HGNECC_97	315	*RICTOR*	63	Known	CN	Amplification

Abbreviations: CN, copy number; N/A, not applicable; RE, rearrangement; SV, structural variation.