SUPPLEMENTARY FIGURE LEGENDS

Figure S1. Sanger sequencing validation of next generation sequencing (NGS) variant calls. **A**. Representative individual read level variant calls from NGS data for a *TP53* c.C1010A (p.R337L) call from sample 9B as visualized using the Integrative Genomics Viewer, with the variant allele (A) highlighted in green. **B**. Sanger chromatogram tracing from the same samples DNA showing the presence of C1010A, confirming the NGS variant call.

Figure S2. Alternative view of integrative molecular profiling heatmap. Heatmap of non-synonymous mutations and high level copy number alterations as shown in **Figure 1** in the text, with the tumor samples (columns) ordered by histologic type and mutational burden and genes represented in rows by decreasing alteration frequency. Clinicopathologic information is indicated in the header as in **Figure 1**.

Figure S3. p16 expression via immunohistochemistry. Medium power (100x) magnification photomicrographs of representative tumor samples with corresponding images of p16 IHC. Sample 42 was found to be HPV negative via PCR (see **Table S3** for details) and showed no p16 expression. Sample 21 was HPV positive by PCR, and showed diffuse p16 staining. Sample 1a showed diffuse p16 expression despite no detectable HPV DNA.

Figure S4. Kaplan-Meier analysis of histologic subtypes of PeSCCA. Outcome analysis was performed for all profiled patients (considering primary specimens if matched primary

tumors/lymph node metastases were profiled) using combined distant progression and PeSCCA specific death as a composite endpoint. **A.** Event free survival curves for high risk (basaloid and warty basaloid), intermediate risk (usual type), and low risk (papillary, verrucous, warty) tumors evaluated with no significant difference in event free survival time (log-rank test P=0.11). **B.** Event free survival curve with high risk and intermediate risk tumors (as described above) combined into one group compared to low risk tumors (log-rank test, P=0.06).

Figure S5. Comparison of prioritized molecular alterations in penile (PN) squamous cell carcinomas (SCCA) compared to other SCCAs. A. The % of samples in this PeSCCA study and TCGA SCCA profiling studies (Lung: Lu; Head and Neck: HN; Cervical: Ce) with prioritized oncogenic/tumor suppressive alterations (classes as in **Fig 1**) in *TP53*, *CDKN2A*, *PIK3CA*, *MYC*, *HRAS*, *CCND1*, *SOX2*, *NFE2L2*, *EGFR* and *KRAS* is given. *P* values from two-sided Fisher's exact tests comparing the frequency of samples with alterations in any of these genes in PeSCC vs. each TCGA SCCA type are indicated. TCGA datasets were accessed through cBioPortal. **B**. Oncoprint visualization of alterations in TCGA SCCA studies from **A**. For each sample in the indicated TCGA study, alterations in the indicated gene are shown according to the legend are indicated (gray indicates no alteration). **C**. Comparison of alteration frequency for each gene in PeSCCA vs. each TCGA study. *P* values from two sided Fisher's exact tests comparing the frequency of samples with alterations in any of these genes in PeSCCA vs. each TCGA SCCA type are indicated.