Table S1. Acceptable ICD10 codes

C00 Malignant Neoplasm of the Lip
C00.0 Malignant neoplasm of external upper lip
C00.1 Malignant neoplasm of external lower lip
C00.2 Malignant neoplasm of external lip, unspecified
C00.3 Malignant neoplasm of upper lip, inner aspect
C00.4 Malignant neoplasm of lower lip, inner aspect
C00.5 Malignant neoplasm of lip, unspecified, inner aspect
C00.6 Malignant neoplasm of commissure of lip, unspecified
C00.8 Malignant neoplasm of overlapping sites of lip
C00.9 Malignant neoplasm of lip, unspecified
C01 Malignant Neoplasm of Base of Tongue
C01 Malignant neoplasm of base of tongue

C02 Malignant Neoplasm of Other and Unspecified Parts of Tongue
C02.0 Malignant neoplasm of dorsal surface of tongue
C02.1 Malignant neoplasm of border of tongue
C02.2 Malignant neoplasm of ventral surface of tongue
C02.3 Malignant neoplasm of anterior two-thirds of tongue, part unspecified
C02.4 Malignant neoplasm of lingual tonsil
C02.8 Malignant neoplasm of overlapping sites of tongue
C02.9 Malignant neoplasm of tongue, unspecified

C03 Malignant Neoplasm of Gum
C03.0 Malignant neoplasm of upper gum
C03.1 Malignant neoplasm of lower gum

C03.9 Malignant neoplasm of gum, unspecified
C04 Malignant Neoplasm of Floor of Mouth
C04.0 Malignant neoplasm of anterior floor of mouth
C04.1 Malignant neoplasm of lateral floor of mouth
C04.8 Malignant neoplasm of overlapping sites of floor of mouth
C04.9 Malignant neoplasm of floor of mouth, unspecified
C05 Malignant Neoplasm of Palate
C05.0 Malignant neoplasm of hard palate
C05.1 Malignant neoplasm of soft palate
C05.2 Malignant neoplasm of uvula
C05.8 Malignant neoplasm of overlapping sites of palate
C05.9 Malignant neoplasm of palate, unspecified

C06 Malignant Neoplasm of Other and Unspecified Parts of Mouth
C06.0 Malignant neoplasm of cheek mucosa
C06.1 Malignant neoplasm of vestibule of mouth
C06.2 Malignant neoplasm of retromolar area
C06.80 Malignant neoplasm of overlapping sites of unspecified parts of mouth

C06.89 Malignant neoplasm of overlapping sites of other parts of mouth

C06.9 Malignant neoplasm of mouth, unspecified
C09 Malignant Neoplasm of Tonsil
C09.0 Malignant neoplasm of tonsillar fossa
C09.1 Malignant neoplasm of tonsillar pillar (anterior) (posterior)
C09.8 Malignant neoplasm of overlapping sites of tonsil
C09.9 Malignant neoplasm of tonsil, unspecified
C10 Malignant Neoplasm of Oropharynx
C10.0 Malignant neoplasm of vallecula
C10.1 Malignant neoplasm of anterior surface of epiglottis
C10.2 Malignant neoplasm of lateral wall of oropharynx
C10.3 Malignant neoplasm of posterior wall of oropharynx
C10.4 Malignant neoplasm of branchial cleft
C10.8 Malignant neoplasm of overlapping sites of oropharynx
C10.9 Malignant neoplasm of oropharynx, unspecified

C12 Malignant neoplasm of pyriform sinus
C12 Malignant neoplasm of pyriform sinus
C13 Malignant Neoplasm of Hypopharynx
C13.0 Malignant neoplasm of postcricoid region
C13.1 Malignant neoplasm of aryepiglottic fold, hypopharyngeal aspect
C13.2 Malignant neoplasm of posterior wall of hypopharynx
C13.8 Malignant neoplasm of overlapping sites of hypopharynx
C13.9 Malignant neoplasm of hypopharynx, unspecified
C14 Malignant Neoplasm of Other and Ill-Defined Sites in the Lip, Oral Cavity, and Pharynx
C14.0 Malignant neoplasm of pharynx, unspecified
C14.2 Malignant neoplasm of Waldeyer's ring

C14.8 Malignant neoplasm of overlapping sites of lip, oral cavity, and pharynx
C30 Malignant Neoplasm of Nasal Cavity and Middle Ear
C30.0 Malignant neoplasm of nasal cavity
C30.1 Malignant neoplasm of middle ear
C31 Malignant Neoplasm of Accessory Sinuses
C31.0 Malignant neoplasm of maxillary sinus
C31.1 Malignant neoplasm of ethmoidal sinus
C31.2 Malignant neoplasm of frontal sinus
C31.3 Malignant neoplasm of sphenoid sinus
C31.8 Malignant neoplasm of overlapping sites of accessory sinuses
C31.9 Malignant neoplasm of accessory sinus, unspecified
C32 Malignant Neoplasm of Larynx

C32.0 Malignant neoplasm of glottis
C32.1 Malignant neoplasm of supraglottis
C32.2 Malignant neoplasm of subglottis
C32.3 Malignant neoplasm of laryngeal cartilage
C32.8 Malignant neoplasm of overlapping sites of larynx

C32.9 Malignant neoplasm of larynx, unspecified

C76 Malignant Neoplasm of Head, Face, and Neck (other and ill-defined sites)
C76.0 Malignant neoplasm of head, face, and neck

Table S2. HUGO gene designations of input genes for model development

C2	PTPRC	HLA-DRA	C1QB	CD3E	FCER1G	C3AR1	CCL4
DOCK8	LILRB4	CCR5	CCL3L3	CXCR3	GZMH	GPR65	CD80
STAT2	DRAM1	IL21R	TNFAIP3	PSMB9	IL15	GBP5	CD300LF
RNF19B	ETV7	CD96	CXCL11	TMEM140	PLAUR	ISG20	IFNG
SLC15A3	GPR171	APOL3	RIPK2	LILRB2	SLA2	ICAM1	SPI1
IFIT2	SIRPG	CCL5	CD69	IL15RA	TRANK1	CD74	DOK2
IFI30	TAP2	IL2RB	TRIM21	HLA-B	WARS	GBP2	STAT4
CXCL10	PARP14	CD163	SP100	SAMSN1	PDCD1	CD2	CD300A
JAK2	FPR3	UHRF2	NLRC5	UBA7	CSF1	LAG3	RANBP6
HAPLN3	SH2D1A	DNAJA1	ZBP1	BTN3A1	IL18BP	CTSL	
PLGRKT	SRGN	BATF2	SIGLEC10	CXCR6	PDCD1LG2	CD3G	
CDC37L1	UBE2L6	CD274	IDO1	DDX58	SAMHD1	GPR84	
EPSTI1	TIGIT	IFIH1	BTN3A3	PPP1R18	ITGAL	CIITA	
HLA-F	FCGR1A	TNFRSF9	GZMA	GBP1	CCL8	C1QC	
ITK	STAT1	SP110	TRIM22	FGL2	STX11	TAP1	
GNLY	SLAMF8	GZMB	HLA-DRB1	NKG7	LAP3	TNFSF13B	
LCP2	IL2RA	FCGR3A	PRF1	GBP3	CTLA4	IRF1	
HAVCR2	APOL6	IFIT3	IL12RB1	MYO7A	CD86	ICOS	
FASLG	GBP4	TLR8	CCR1	STK10	CXCL9	PLA2G7	
RNF213	CD8A	FCGR2A	PTPN22	B2M	RIC1	SAMD9L	

Table S3: Excluded Patient Samples

None (included in study)	211
Unacceptable Treatment Regimen	39
Excessive Time to Treatment	18
Unacceptable Specimen Site	17
Incomplete Data	14
Insufficient Material	10
Other Ineligible*	18
Tumor cellularity	48
Fail RNA QC	13
Fail Library QC	10
Fail Analytical QC	15
Withdrawn	2
Total	**415**

Note:
*Includes excluded diagnoses, inconsistent data, site sending wrong material, and other violations of inclusion/exclusion criteria

Table S4. Inclusion/exclusion criteria

Inclusion criteria:	
1.	Subject must have been diagnosed with recurrent or metastatic head and neck squamous cell carcinoma (RM-HNSCC).
2.	Subject must have received, or been scheduled to receive, at least one dose of anti-PD-1 immunotherapy for treatment of their cancer.
3.	Subject must have received, or been scheduled to receive, anti-PD-1 treatment on one of the following regimes: A. Pembrolizumab or nivolumab as a single agent (monotherapy) B. Pembrolizumab or nivolumab in combination with platinum chemotherapy, with or without fluorouracil or a taxane (chemo-immunotherapy)
4.	Subject must have had, or will have had, a tumor biopsy prior to treatment with anti-PD-1 immunotherapy (specimen is considered pre-treatment).
5.	Clinician must have evaluated, or will have evaluated, tumor response to anti-PD-1 immunotherapy using (1) imaging data performed to assess response to anti-PD-1 treatment and/or (2) clinical assessment. Imaging data must include both (a) pre-anti-PD-1-treatment imaging and (b) imaging performed after the start of anti-PD-1 treatment).
6.	Subject is willing to provide informed consent per IRB-approved protocol.
7.	Subject must have sufficient tissue available to fulfill the specimen requirements of the study.
8.	Subject is 18 years of age or older.
Exclusion criteria:	
1.	Subjects who did not have head and neck squamous cell carcinoma (other histologies).
2.	Subjects who only received anti-PD-1 immunotherapy in the newly diagnosed, curative setting.
3.	Subjects who received anti-PD-1 immunotherapy in combination with a treatment other than platinum chemotherapy (with or without fluorouracil or a taxane).
4.	Subjects whose response to anti-PD-1 immunotherapy is not available either as (a) clinician's evaluation of that response or (b) imaging data that was performed to assess response to anti-PD-1 immunotherapy.

Table S5. OncoPrism-HNSCC model is not predictive in non-ICI datasets

dataset	Number of samples	OncoPrism-HNSCC model
TCGA-HNSC	500	0.32
GSE65858	290	0.66
GSE40774	90	0.56
GSE41613	97	0.71

*Notes: the p-values represent p-values for log rank test done on a Cox proportional hazards model.

Table S6. PD-L1 performance metrics

Cohort	Comparison	Accuracy	PPV*	NPV*	Sensitivity	Specificity
Cohort 1 (monotherapy)	CPS<1 vs CPS≥1	52%	48%	75%	93%	18%
Cohort 1 (monotherapy)	CPS<20 vs CPS≥20	58%	55%	60%	43%	71%
Cohort 2 (chemo-immunotherapy)	CPS<1 vs CPS≥1	60%	61%	50%	90%	15%
Cohort 2 (chemo-immunotherapy)	CPS<20 vs CPS≥20	60%	76%	52%	45%	81%

*Notes: PPV=positive predictive value; NPV=negative predictive value

Table S7: Comparison of OncoPrism and PD-L1 CPS

	PD-L1 TP	PD-L1 FN	PD-L1 TN	PD-L1 FP
OncoPrism TP	33	1	-	-
OncoPrism FN	21	3	-	-
OncoPrism TN	-	-	8	32
OncoPrism FP	-	-	1	13

Abbreviations:
TP, True Positive, correctly predicted disease control;
FN, False Negative, disease control incorrectly predicted as no disease control;
TN, True Negative, correctly predicted no disease control;
FP, False Positive, no disease control incorrectly predicted as disease control

Table S8: Comparison of OncoPrism and TMB

	TMB TP	TMB FN	TMB TN	TMB FP
OncoPrism TP	2	9	-	-
OncoPrism FN	1	1	-	-
OncoPrism TN	-	-	10	0
OncoPrism FP	-	-	9	0

Abbreviations:
TP, True Positive, correctly predicted disease control;
FN, False Negative, disease control incorrectly predicted as no disease control;
TN, True Negative, correctly predicted no disease control;
FP, False Positive, no disease control incorrectly predicted as disease control

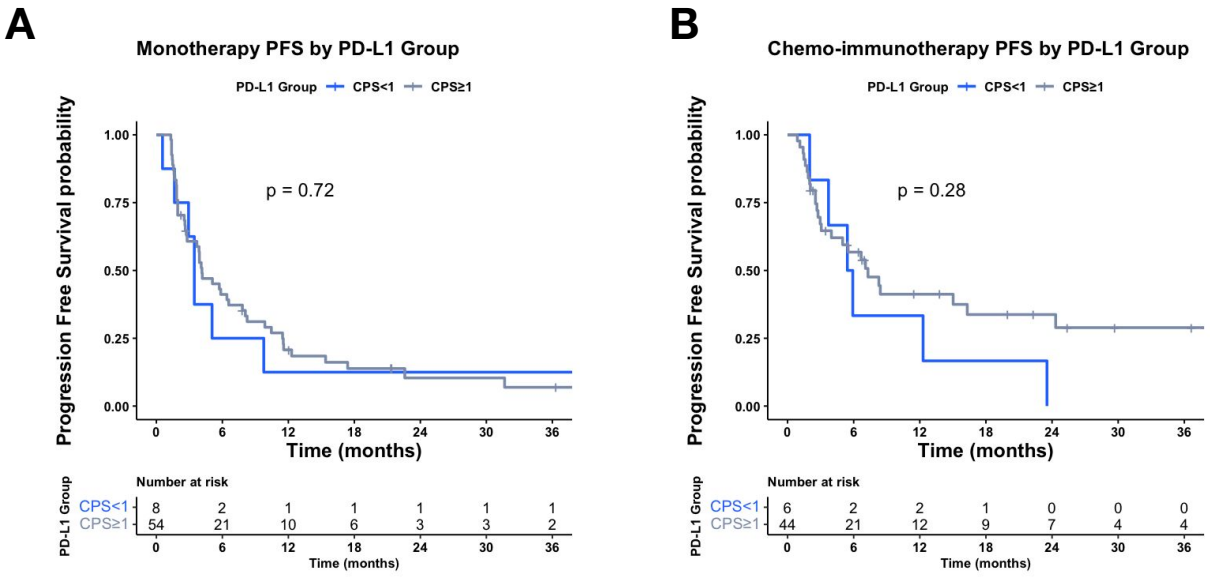

Figure S1. PD-L1 does not predict progression-free survival (PFS). Patients were divided into PD-L1 CPS<1 or CPS≥1 groups within each validation cohort. PD-L1 status was not significantly correlated with PFS in the monotherapy (p=0.71) **(A)** or chemo-immunotherapy (p=0.28) **(B)** validation cohorts. P-values for PFS were calculated using log rank methods.

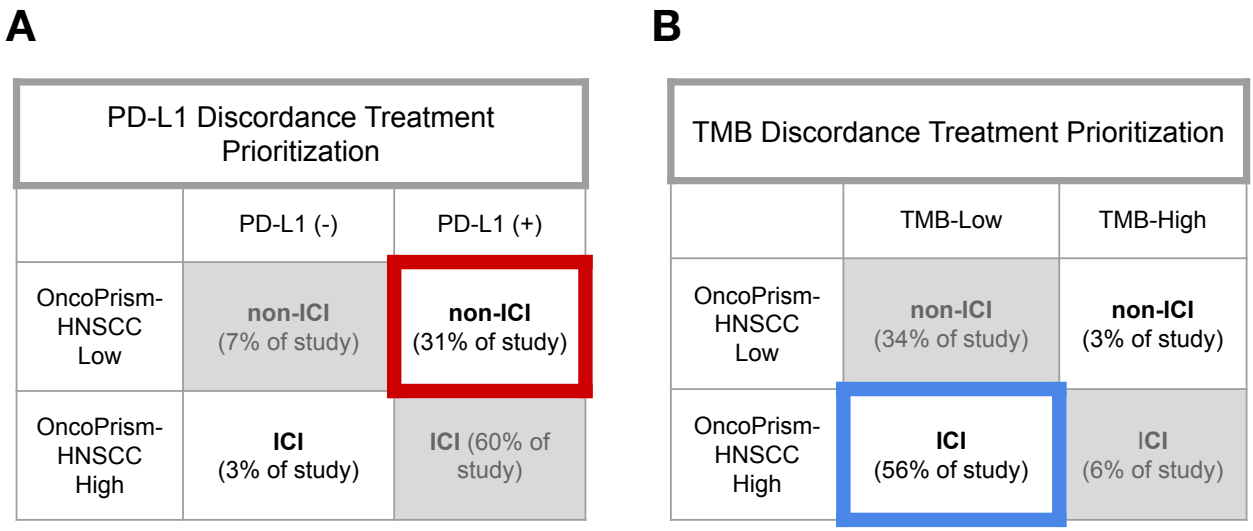

Figure S2. Treatment prioritization for discordant test results. The recommended treatment for concordant (grey) and discordant (white) test results is shown for OncoPrism-HNSCC compared to PD-L1 CPS (**A**) or TMB (**B**). The percent shown is the percentage of the study population in each category. The most common discordant test results are outlined for PD-L1 (red) and TMB (blue). OncoPrism Medium samples were considered indeterminate and are not included. For comparison with PD-L1, n=75. For comparison with TMB, n=32.

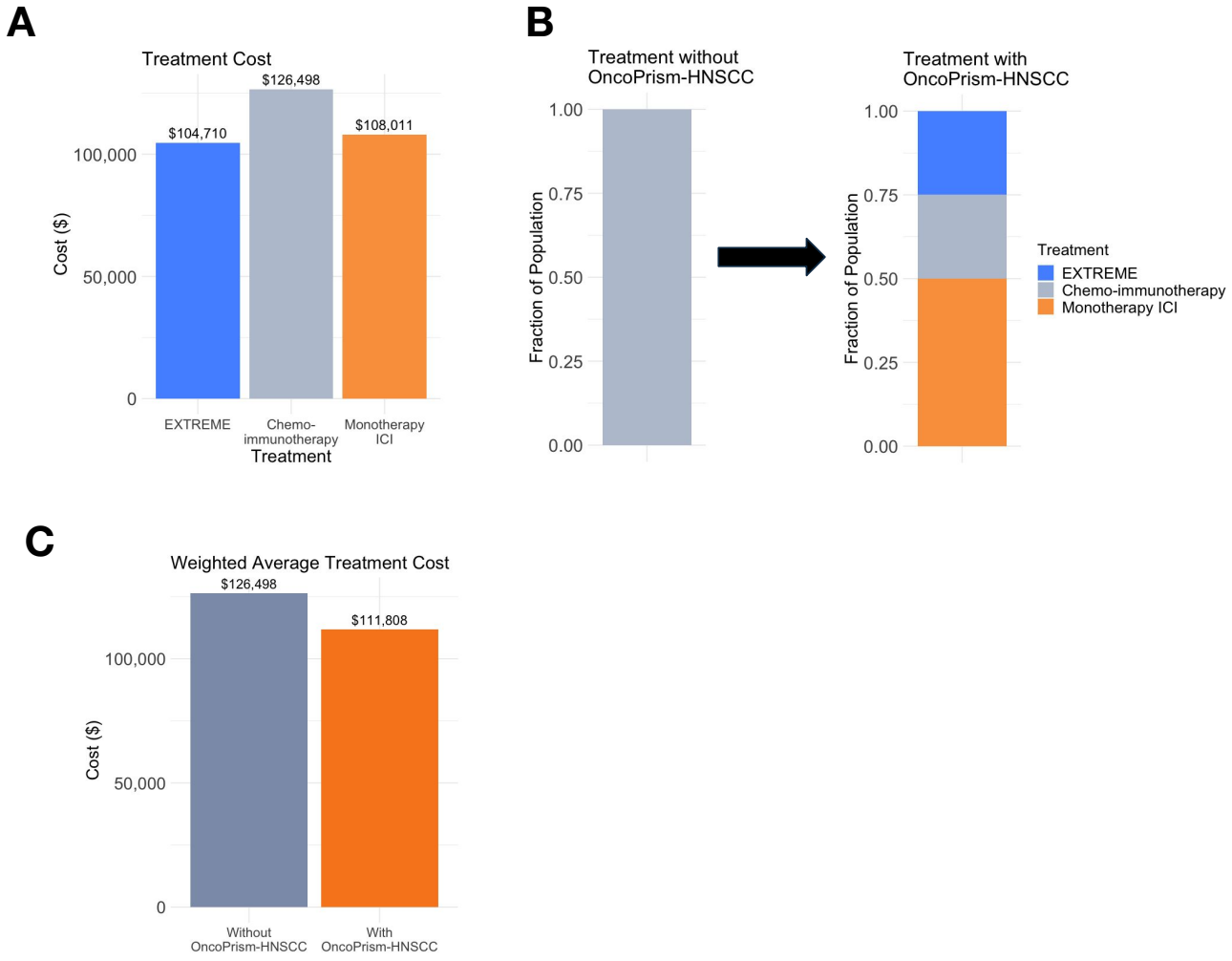

Figure S3. The health economics of OncoPrism-HNSCC testing were modeled using **(A)** published costs for three RM-HNSCC treatment options (EXTREME, chemo-immunotherapy, and monotherapy ICI; Lang et al., 2020). **(B)** The modeling assumed a default treatment plan of chemo-immunotherapy for 100% of patients in the absence of OncoPrism-HNSCC testing (left). With OncoPrism-HNSCC testing (right), the model assumed a treatment distribution of 25% EXTREME, 25% chemo-immunotherapy, and 50% monotherapy ICI, based on the expected proportions of patients in the OncoPrism Low, Medium, and High Groups, respectively. **(C)** The weighted average cost per patient was calculated by multiplying the assumed treatment proportions by the cost of each treatment, resulting in an average savings of $14,691 per OncoPrism-HNSCC tested patient.