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## Supplementary figure legends

Supplementary Figure 1. HPV- exploratory set patient samples grouped by GO term enrichment based on IPL (A), CNA (B), or RNA (C). The selection threshold was lowered to  $\geq$  3 (B) or  $\geq$  60% (C) to include more GO terms to avoid bias.

Supplementary Figure 2. HPV+ exploratory set patient samples grouped by GO term enrichment based on CNA (A) or RNA (B). The selection threshold was lowered to  $\ge 2$  (A) or  $\ge 60\%$  (B) to include more GO terms to avoid bias.

Supplementary Figure 3. HPV+ exploratory set patient samples grouped by MPAC's input RNA states. (A) Clustering results by K-means under a pre-specified total number of groups ranging from two to six; (B) Clustering results by K-means with a pre-specified six groups; (C–G) Top significantly enriched GO terms in group I (C), II (D), III (E), IV (F), and V (G). The selection threshold was lowered to  $\geq$  95% (F),  $\geq$ 70% (G), or  $\geq$ 50% (C–E) in order to include more GO terms to avoid bias.

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## Supplementary Figure 4. HPV+ exploratory set patient samples grouped by MPAC's input

**CNA states. (A)** Clustering results by K-means under a pre-specified total number of groups ranging from two to six; (**B**) Clustering results by K-means with a pre-specified six groups. Group III, IV, V, and VI contained one sample each.

Supplementary Figure 5. CNA, RNA, and pathway states of CD28 (A), CD86 (B), and LCP2 (C), as well as pathway states of their pathway network neighbors in the eleven group I patients.

Supplementary Figure 6. CNA, RNA, and pathway states of TYK2 (A) and IL12RB1 (B), as well as pathway states of their pathway network neighbors in the eleven group I patients.

Supplementary Figure 7. CNA, RNA, and pathway states of CD247 (A) and FASLG (B), as well as pathway states of their pathway network neighbors in the eleven group I patients.

Supplementary Figure 8. CNA, RNA, and pathway states of FASLG as well as pathway states of its pathway network neighbors in a group I patient TCGA-CR-7385.

Supplementary Figure 9. Overall survival of HPV+ exploratory set patient samples stratified by the inferred pathway levels (IPLs) of proteins from the same submodule (A) or individual protein (B). Not all overall survival tests were statistically significant under a P < 0.01 cutoff. bioRxiv preprint doi: https://doi.org/10.1101/2024.06.15.599113; this version posted June 17, 2024. The copyright holder for this preprint (which was not certified by peer review) is the author/funder, who has granted bioRxiv a license to display the preprint in perpetuity. It is made available under aCC-BY 4.0 International license.

Supplementary Figure 10. Progression-free survival of HPV+ exploratory set patient samples stratified by the inferred pathway levels (IPLs) of all the seven proteins combined (A); proteins from the same submodule (B), or individual protein (C). Not all progression-free survival tests were statistically significant under a P < 0.01 cutoff.

Supplementary Figure 11. Immune cell compositions stratified by the inferred pathway levels (IPLs) of all the seven proteins combined for HPV+ exploratory (A) and validation (B) set. Adjusted Wilcoxon test P on the cell composition difference between two groups of patient samples were shown for each cell type. Eosinophil was not found in either the exploratory or validation sets. T cell CD4+ naïve was not found in the validation set.

Supplementary Figure 12. Overall survival of HPV+ validation set patient samples stratified by the inferred pathway levels (IPLs) of proteins from the same submodule (A) or individual protein (B). Not all overall survival tests were statistically significant under a P < 0.01 cutoff.



## 322 patient samples in HPV- exploratory set by CNA

-3 -2 -1 0

-4



В

glutathione derivative biosynthetic process glutathione metabolic process phosphatidylglycerol acyl-chain remodeling phosphatidylserine metabolic process blood coagulation, fibrin clot formation proteolysis cellular component disassembly chemokine-mediated signaling pathway monosaccharide metabolic process retinoic acid metabolic process G protein-coupled purinergic nucleotide receptor signaling pathway extracellular matrix disassembly collagen catabolic process cellular glucuronidation



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71 patient samples in HPV+ exploratory set by CNA

71 patient samples in HPV+ exploratory set by RNA

Ш

IV



В

42 GO terms significantly over-represented in ≥ 60% samples in a group

T

II









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11 group I patient samples in HPV+ exploratory set



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0.50

0.25

0.00

÷

1.00 0.75 0.50 0.25

0.00

0

overall survival probability

0

p = 0.01

1000 2000 3000

days

+ FASLG>0 (n=30)

others (n=41)

p = 0.0058

1000 2000 3000

days

0.50

0.25

0.00

= 0.0033

1000 2000 3000

days

D

0

overall

A CD28>0 (n=25) CD28>0 (n=25)



A (which was not certifie 71 patie	: https://doi.org/10.1101/2024.06.15.599 d by peer review) is the author/funder, w ent samples in HPV+ <b>explorted</b> .	113; this version posted June 17, 2024. The copyri ho has granted bioRxiv a license to display the pre aCC-BY 4.0 International license. 18 pati	ght holder for this preprint print in perpetuity. It is made ent samples in HPV+ validation set
申 all submodule 卓 others (n=56	e protein IPLs > 0 (n=15) Wilcoxon te adjusted P	st	e protein IPLs > 0 (n=3) Wilcoxon tes adjusted P
T cell follicular helper -	2.3e-05	T cell follicular helper -	0.3
T cell CD8+ -	2.3e-05	T cell CD8+ -	0.3
Macrophage M1 -	2.3e-05	NK cell activated -	0.3
Macrophage M2 -	0.00065	Macrophage M2 -	0.3
T cell regulatory (Tregs) -	0.00075	Macrophage M1 -	0.3
NK cell activated -	<b>9</b> .0012	T cell CD4+ memory activated -	<b>•</b> 0.45
B cell naive -	<b>L</b> 0.0012	T cell regulatory (Tregs) -	<b>•</b> 0.47
T cell CD4+ memory resting -	0.0052	T cell gamma delta -	<b>L</b> — 0.47
NK cell resting -	<b>₽</b> 0.0052	Mast cell activated -	<b>E</b> 0.47
B cell memory -	<b>L</b> 0.0052	B cell plasma -	0.47
Myeloid dendritic cell resting -	<b>5</b> 0.016	NK cell resting -	0.53
Monocyte -	<b>6</b> .042	Mast cell resting -	0.56
B cell plasma -	0.078	Neutrophil -	0.74
T cell CD4+ memory activated -	<b>E</b> 0.31	Myeloid dendritic cell activated -	0.74
T cell gamma delta -	0.4	Monocyte -	<b>b</b> 0.74
T cell CD4+ naive -	0.4	Macrophage M0 -	0.74
Neutrophil -	0.4	B cell naive -	0.74
Myeloid dendritic cell activated -	<b>8</b> = 0.4	T cell CD4+ memory resting -	0.8
Mast cell activated -	<b>E</b> — 0.4	Myeloid dendritic cell resting -	<b>•</b> 0.9
Macrophage M0 -	0.4	B cell memory -	0.9
Mast cell resting -	<b>B</b> 0.44	T cell CD4+ naive -	nonexistent
Eosinophil -	nonexisten	t Eosinophil -	nonexistent
cell f	20% 40% raction (CIBERSORT-ABS score)	cell f	20% raction (CIBERSORT-ABS score)

