

# HPVTIMER: 一个用于探索 HPV相关肿瘤的肿瘤免疫 微环境的shiny网页工具



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网页工具地址：<http://www.hpvtimer.com/>

Liying Liu, Yanan Xie, Hong Yang, Anqi Lin, Minjun Dong, Haitao Wang, Cangang Zhang, Zaoqu Liu, Quan Cheng, Jian Zhang, Shuofeng Yuan, Peng Luo. 2023. HPVTIMER: A Shiny web application for tumor immune estimation in human papillomavirus-associated cancers. *iMeta* 1: e1. <https://doi.org/10.1002/imt2.130>

# 亮点摘要

- HPVTIMER基于转录组数据，开发了4个可用于探索不同癌种的HPV阳性样本和HPV阴性样本之间的差异的模块：差异表达分析，相关性分析，免疫浸润分析和通路分析。
- 免疫浸润分析模块提供7种免疫浸润算法
- HPVTIMER支持用户开展meta分析，可用于探索在整体样本中基因表达量/通路ssGSEA评分/免疫浸润评分之间的相关性以及HPV阳性/阴性样本之间免疫浸润评分的差异。

# 引言

## ● 关于HPV相关肿瘤和免疫治疗

人乳头瘤病毒（HPV）相关肿瘤是指与高危型HPV感染相关的，发生在不同部位却具有**相似的生物学和免疫学特性**的肿瘤。

但是许多研究表明，在经过新型免疫疗法靶向治疗后，患者疾病的缓解率较低，且存在继发性耐药。

HPV相关肿瘤的免疫微环境具有许多相似之处。但不同原发部位的HPV相关肿瘤**具有不同的临床特征**。

## ● 关于HPV相关肿瘤数据和网页工具

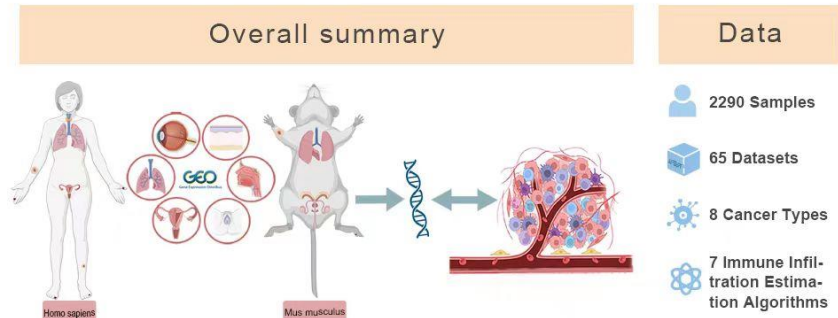
公开数据库上有许多HPV相关肿瘤的转录组数据，**但对于没有免疫浸润分析专业知识的用户来说**，难以从中提取相关信息。

现有相关分析平台和网页工具存在的限制

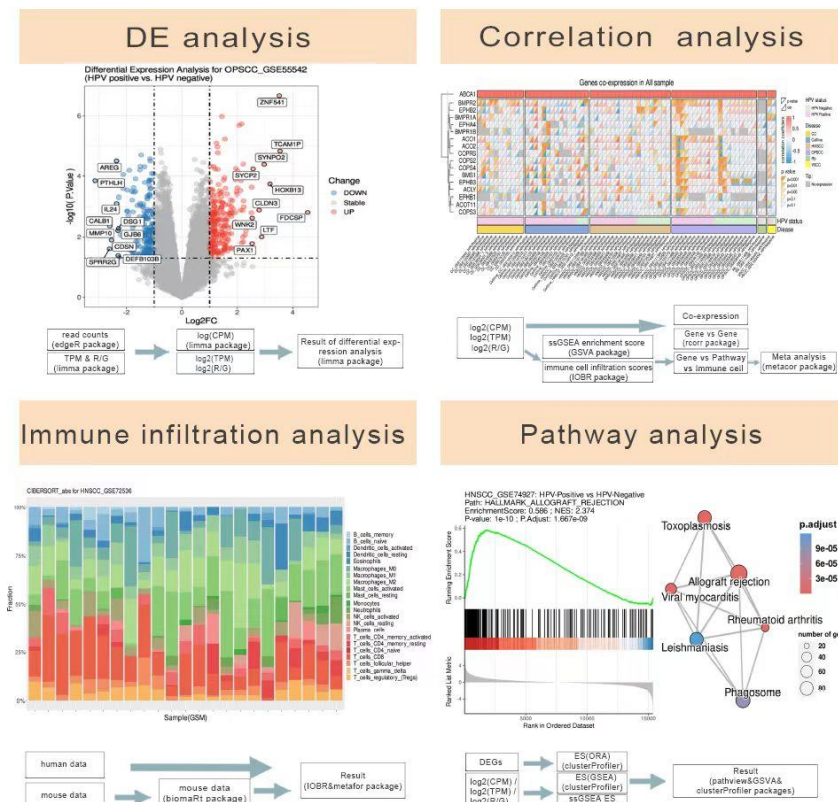
- TME研究工具：如CancerImmunityQTL、TIP和TIMER2.0
- 单一癌症的研究工具：CCDB；HNCDB，HNdb；OrCGDB
- 病毒研究工具：如VISDB

## HPVTIMER: HPV-associated Tumor Immune Micro-Environment ExploreR

Data preparing

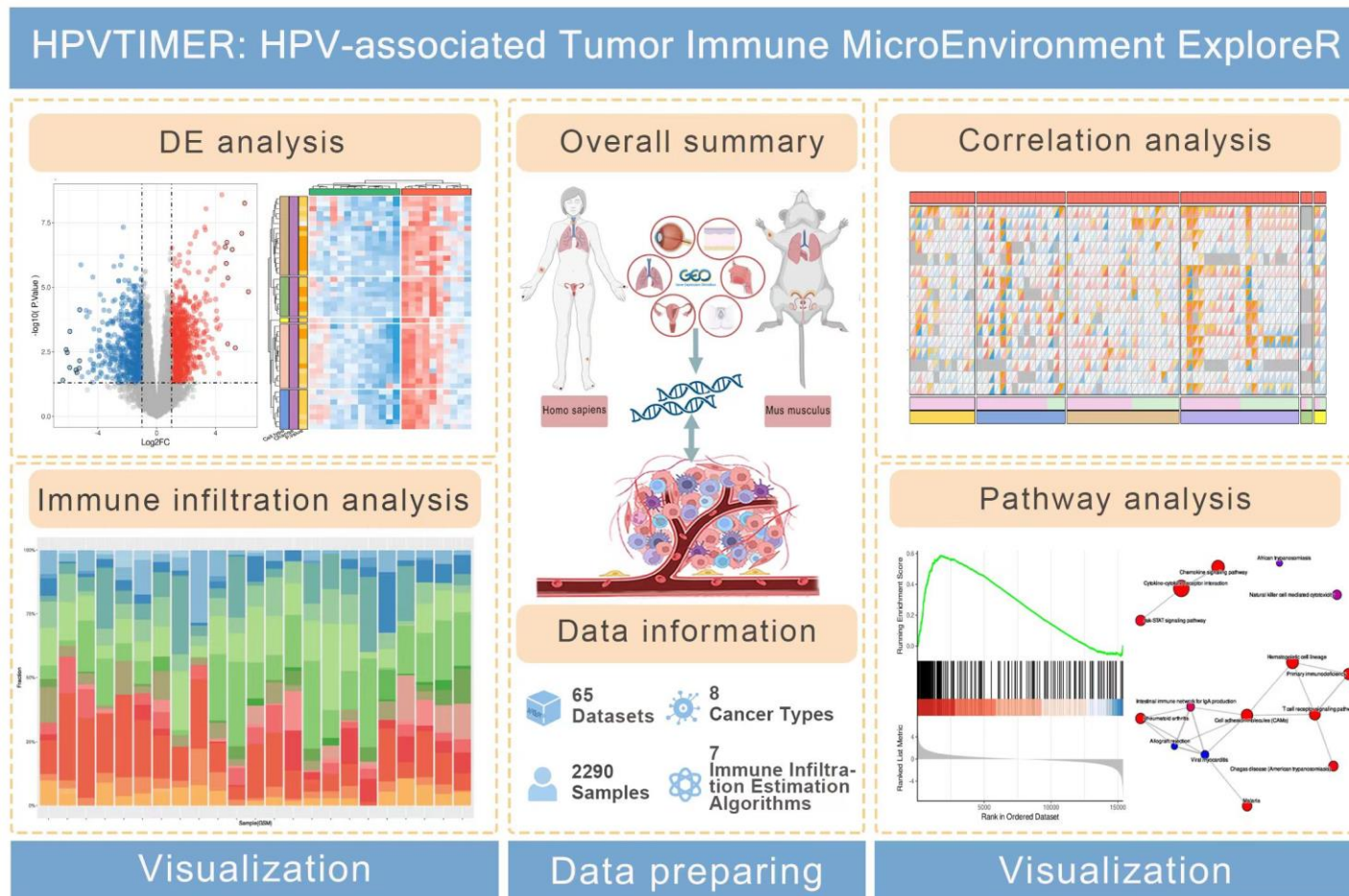


Visualization



# 结果

- 网站链接: <http://www.hpvtimer.com/>
- 内置了2290个样本, 65个HPV相关肿瘤的转录组数据集, 涵盖8个肿瘤类型和2个物种
- 提供了4个分析模块, 即差异表达分析模块、相关性分析模块、免疫浸润分析模块和通路分析模块



# 结果

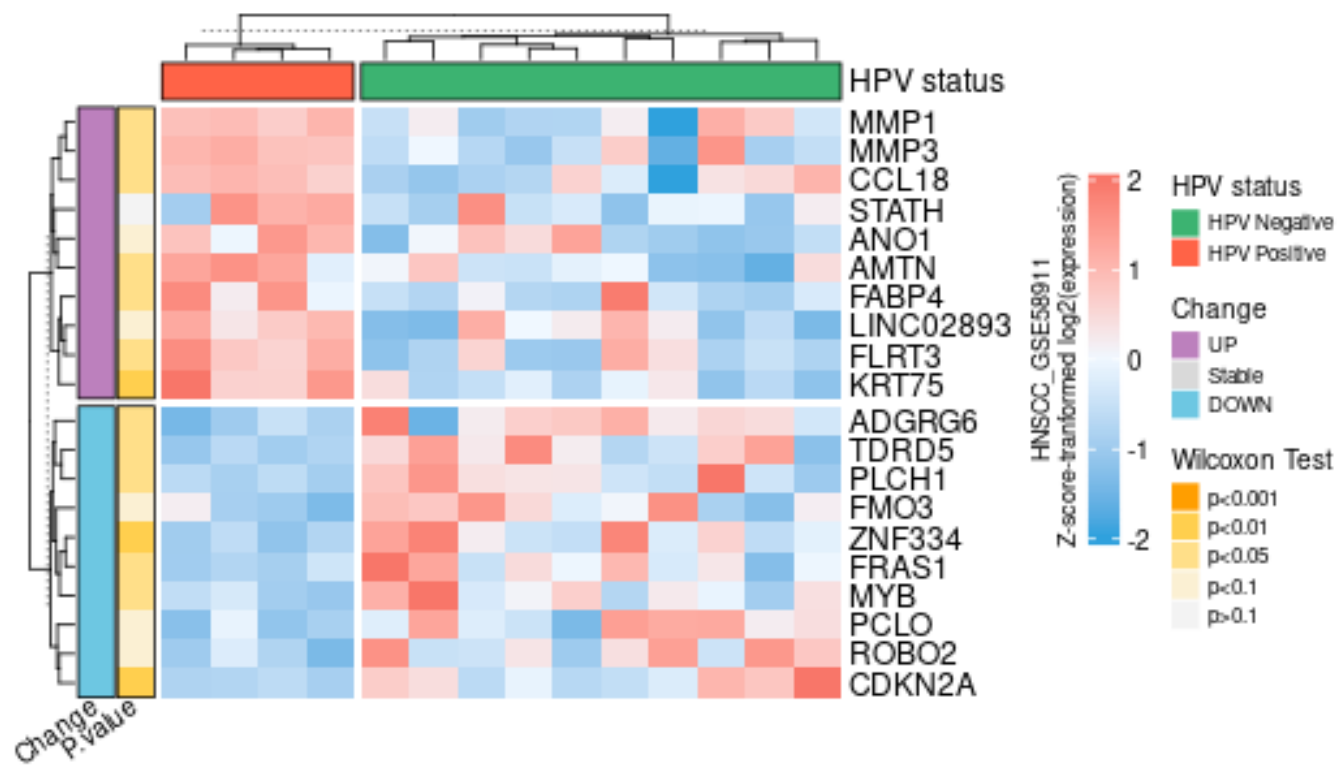
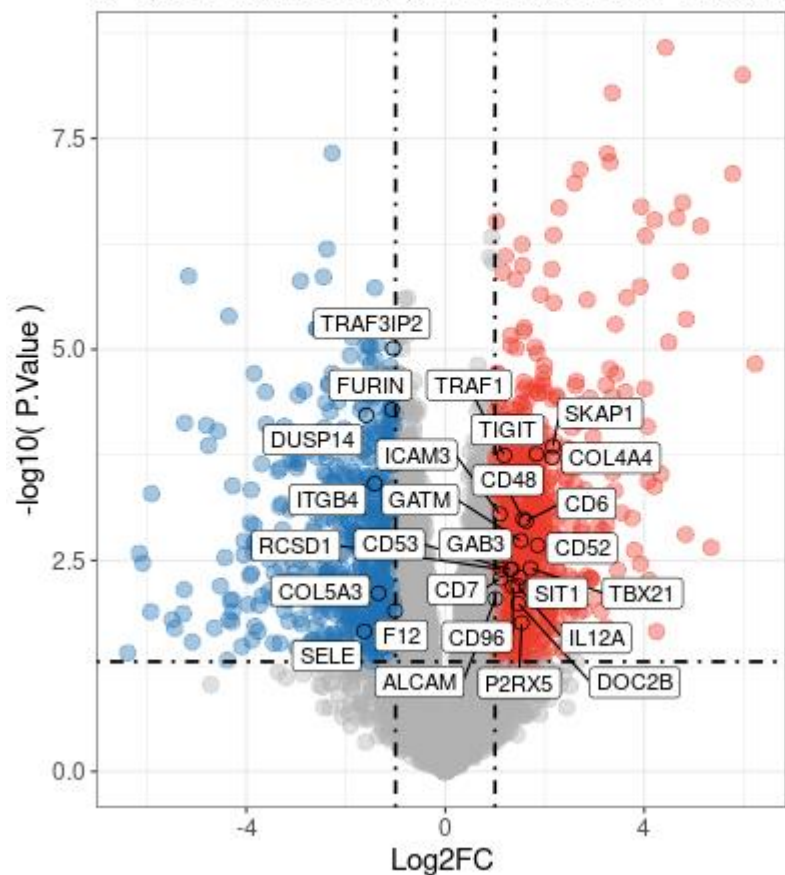
- 差异表达分析 (DE analysis)
- 3个子模块: Overall, Immune cells, Pathways
- 3种可视化: 火山图, 热图, 箱线图
- 自定义分析参数及绘图参数

The screenshot displays the HPVTIMER web application interface. The main title is "Differential Expression Analysis for Immune Cell". The interface is divided into three tabs: "Volcano", "Heatmap", and "Boxplot". The "Volcano" tab is currently selected. The interface includes a search bar for datasets, currently showing "HNSCC\_GSE72536 (n=23)", and a dropdown for selecting an immune cell, currently showing "Type 1 T helper cell". A "Visualize" button is present. Below these are customization options for the threshold of P.Value or adj.P.Val (set to 0.05) and the threshold of |log2FC| (set to 1). The "Volcano Color" section shows three color-coded categories: UP (red, #EF3B2C), Stable (grey, #B2B2B2), and DOWN (blue, #2171B5). The footer contains the copyright notice: "Copyright © 2023. All rights reserved."

# 结果

## ● 差异表达分析 (DE analysis)

Differential Expression Analysis for HNSCC\_GSE72536  
in Type 1 T helper cell (HPV positive vs. HPV negative)



# 结果

## ● 相关性分析 (Correlation)

● 4个子模块: **Co-expression, Multi-genes, Scatter plot, Meta analysis**

● 5种可视化: 共表达热图, 散点图, 相关性矩阵图, 气泡矩阵图, 森林图

● 自定义分析参数及绘图参数

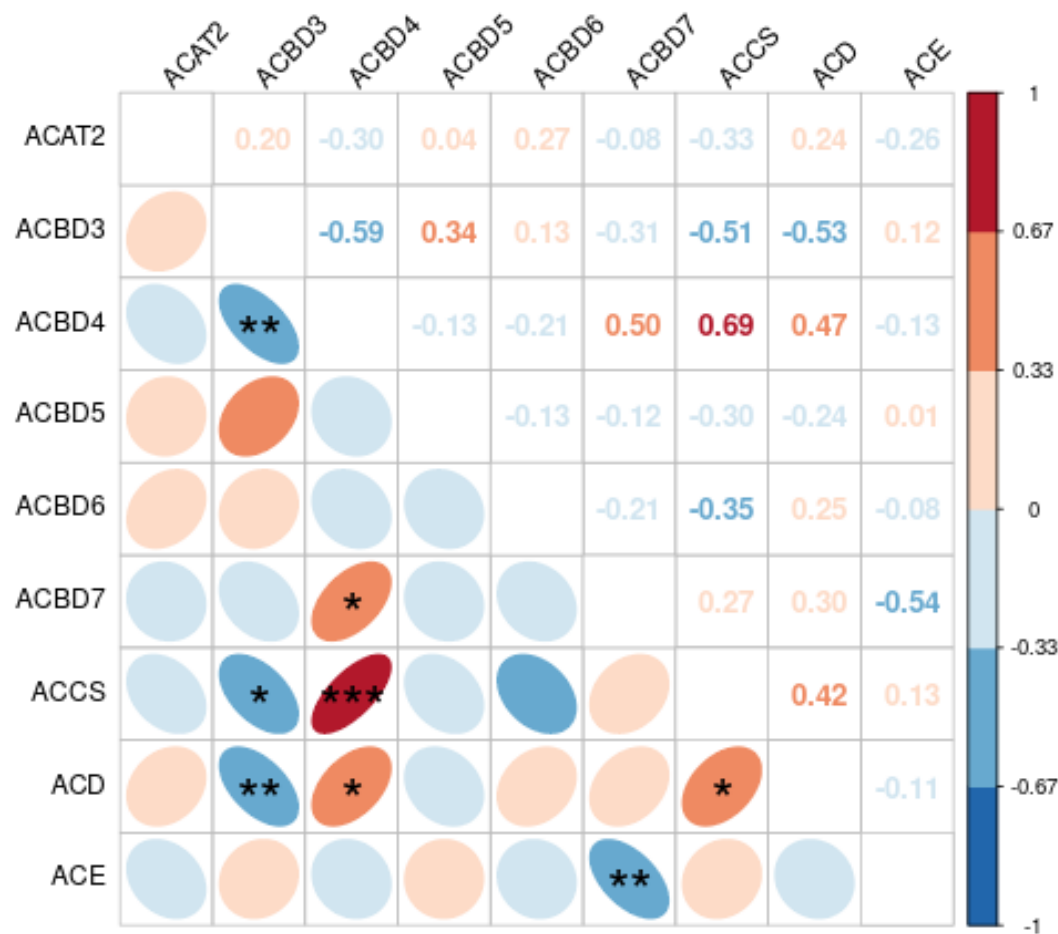
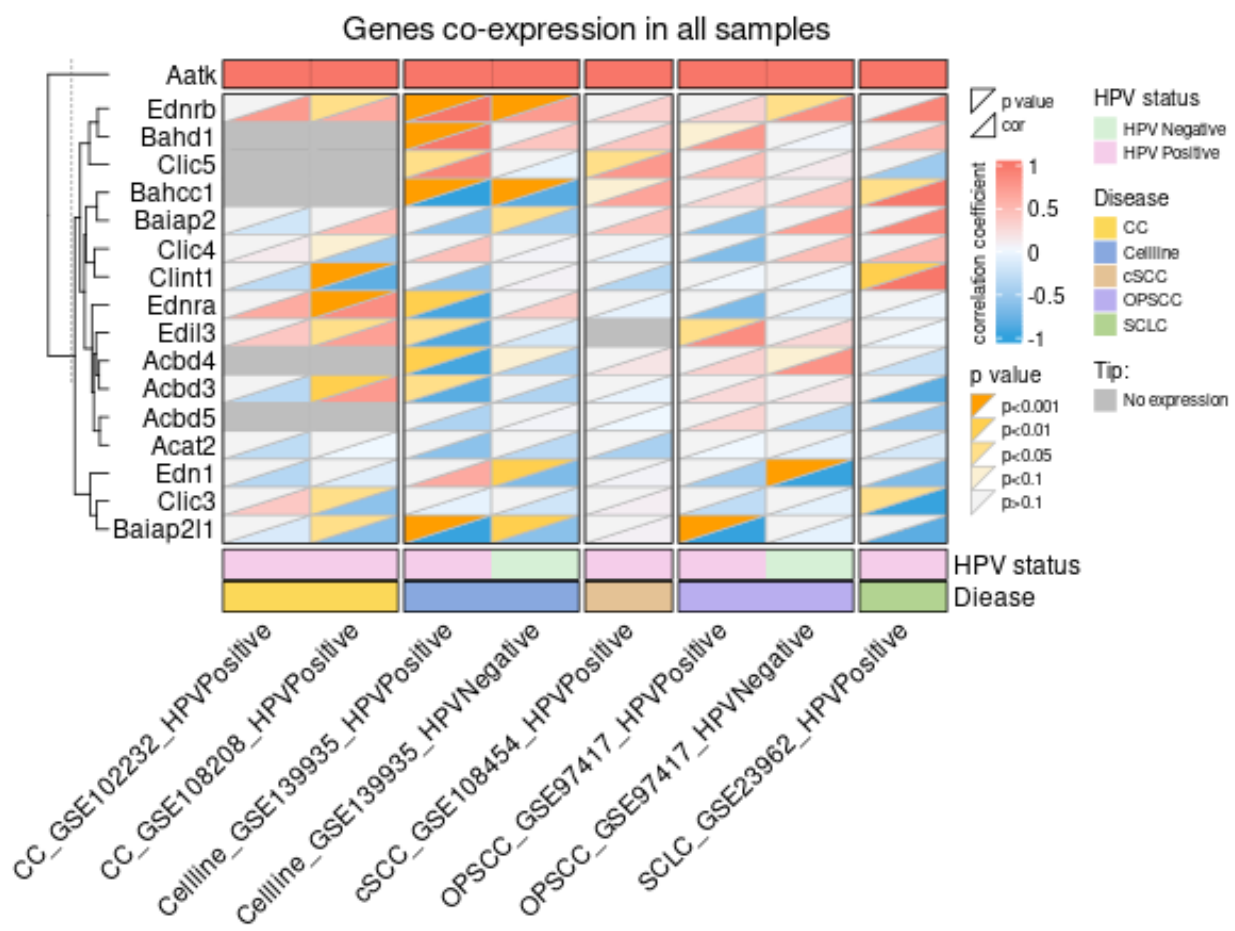
The screenshot shows the HPVTIMER web application interface for Co-Expression analysis. The left sidebar contains navigation options: Introduction, DE analysis, Correlation, Co-expression (selected), Scatter plot, Multi-genes, Meta analysis, Immune infiltration, Pathway analysis, Data, and About. The main content area is titled "Co-Expression" and includes the following settings:

- Select the species:**  Homo sapiens  Mus musculus
- Select a method for correlation:**  Pearson  Spearman
- Search, select a key gene symbol:** ABCA1
- Correlation with the key gene:** A list of genes including ACLY, ACO1, ACO2, ACOT11, BMPR1A, BMPR1B, BMPR2, BMS1, COPRS, COPS2, COPS3, COPS4, EPHA4, EPHB1, EPHB2, and EPHB3.
- Select the sample range for analysis:**  HPV\_Positive  HPV\_Negative  All
- Color Option - Select colorscale:** light Red-Blue
- Visualize** button

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# 结果

## ● 相关性分析 (Correlation)



# 结果

- 免疫浸润分析 (Immune infiltration)
- 7种免疫浸润估计算法: CIBERSORT、CIBERSORT absolute mode、MCP-counter (或适用于小鼠数据的mMCP-counter)、EPIC、xCell、quanTIseq和TIMER
- 2个子模块: Immune cells, Meta analysis
- 4种可视化图: 堆积图, 热图, 箱线图, 森林图

The screenshot shows the HPVTIMER web interface for Immune Infiltration Analysis. The interface is divided into a left sidebar and a main content area. The sidebar contains navigation links: Introduction, DE analysis, Correlation, Immune infiltration (expanded), Immune cells, Meta analysis, Pathway analysis, Data, and About. The main content area is titled "Immune Infiltration Analysis" and features four visualization options: Stacked plot, Heatmap, Boxplot, and Multi-datasets. The "Boxplot" option is currently selected. The main content area contains several input fields and a "Visualize" button. The "Which algorithm are you interested in?" dropdown is set to "MCPcounter". The "Search, select an immune cell:" dropdown is set to "T\_cells". The "Search, select 1-5 dataset(s):" field contains four datasets: HNSCC\_GSE72536 (n=23), HNSCC\_GSE74927 (n=36), CC\_GSE113942 (n=7), and CC\_GSE122697 (n=11). The "Color Option" section shows "HPV Positive" as #E69F00 and "HPV Negative" as #999999. The "Visualize" button is located at the bottom right of the main content area.

HPVTIMER

## Immune Infiltration Analysis

Stacked plot | Heatmap | **Boxplot** | Multi-datasets

Which algorithm are you interested in: **MCPcounter**

Search, select an immune cell: **T\_cells**

Search, select 1-5 dataset(s):  
HNSCC\_GSE72536 (n=23)  
HNSCC\_GSE74927 (n=36) | CC\_GSE113942 (n=7)  
CC\_GSE122697 (n=11)

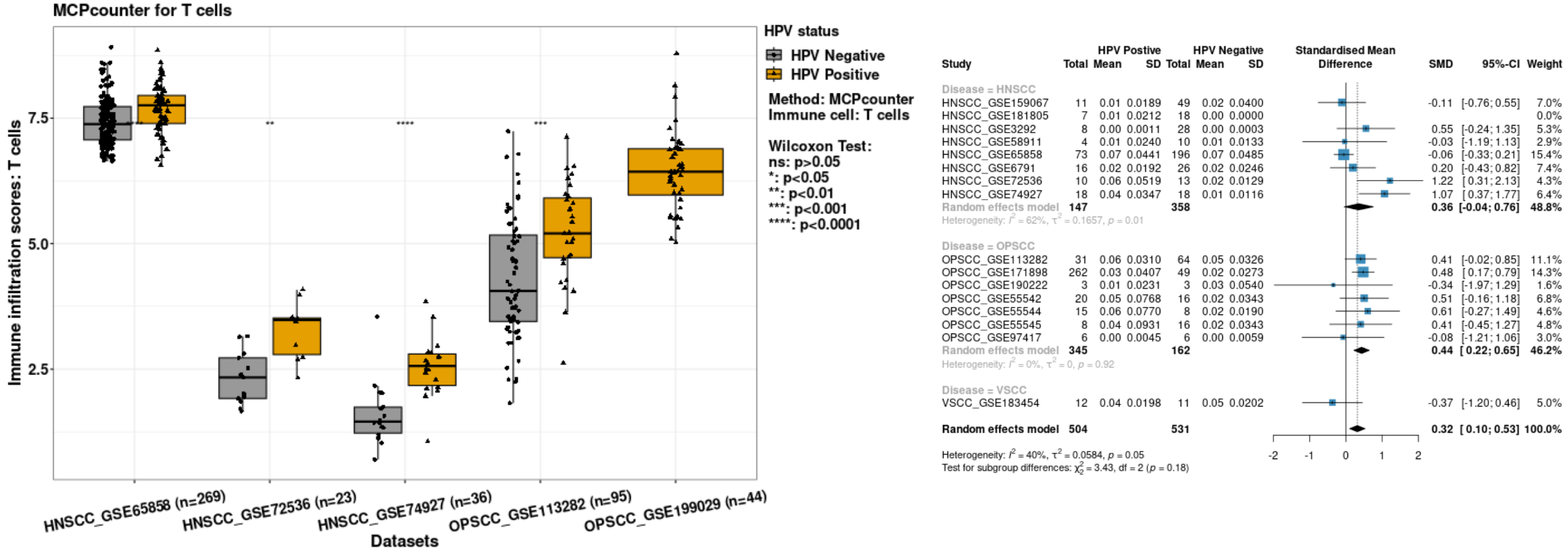
Color Option —  
HPV Positive: **#E69F00** | HPV Negative: #999999

Visualize

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# 结果

## ● 免疫浸润分析 (Immune infiltration)



# 结果

- 通路分析 (Pathway analysis)

- 3个子模块: **Pathway enrichment, Pathview, ssGSEA**

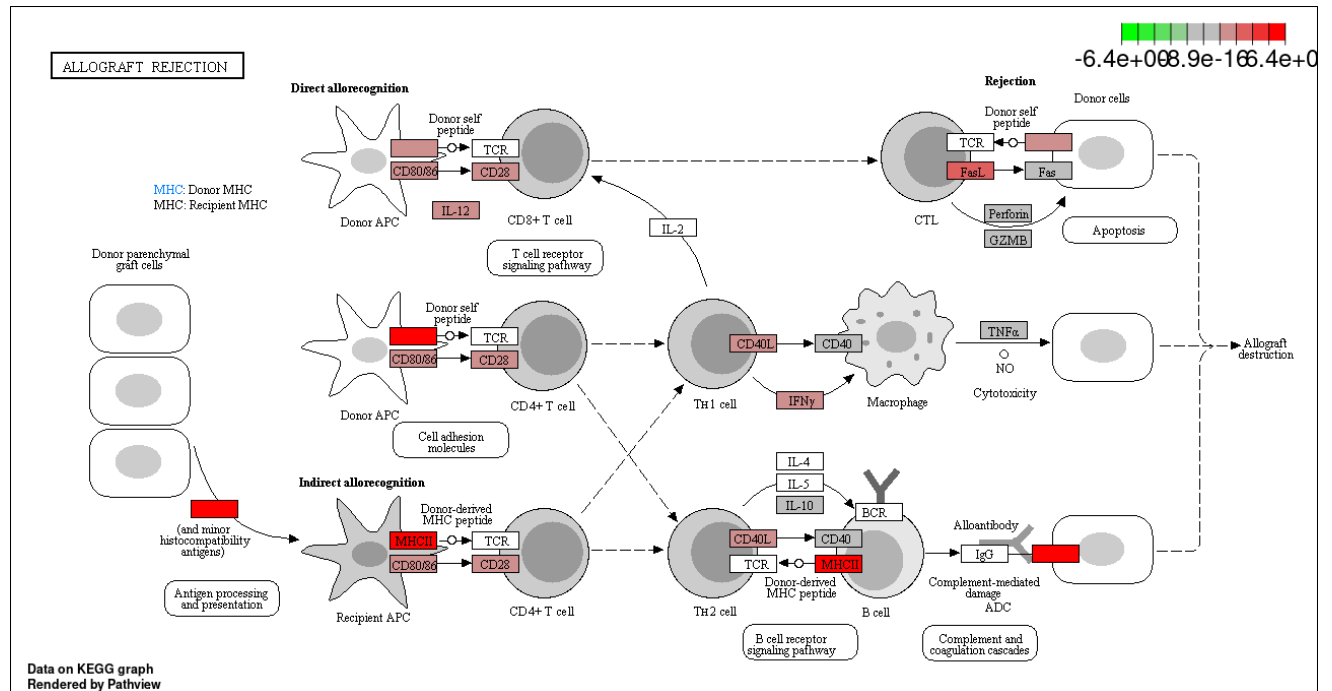
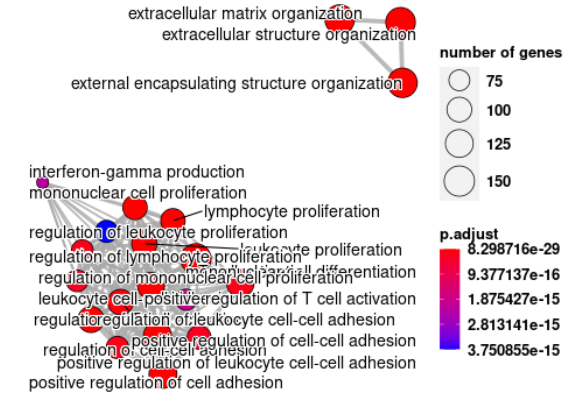
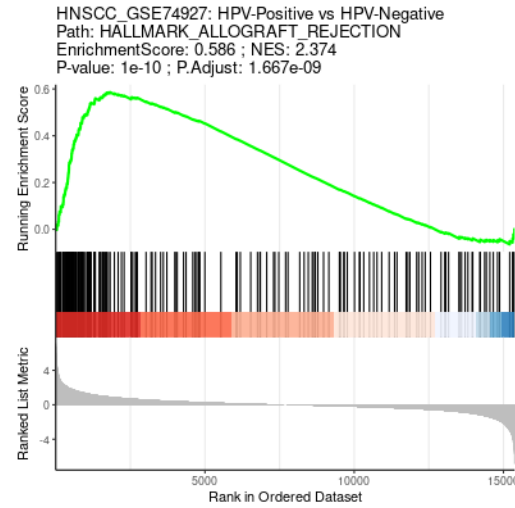
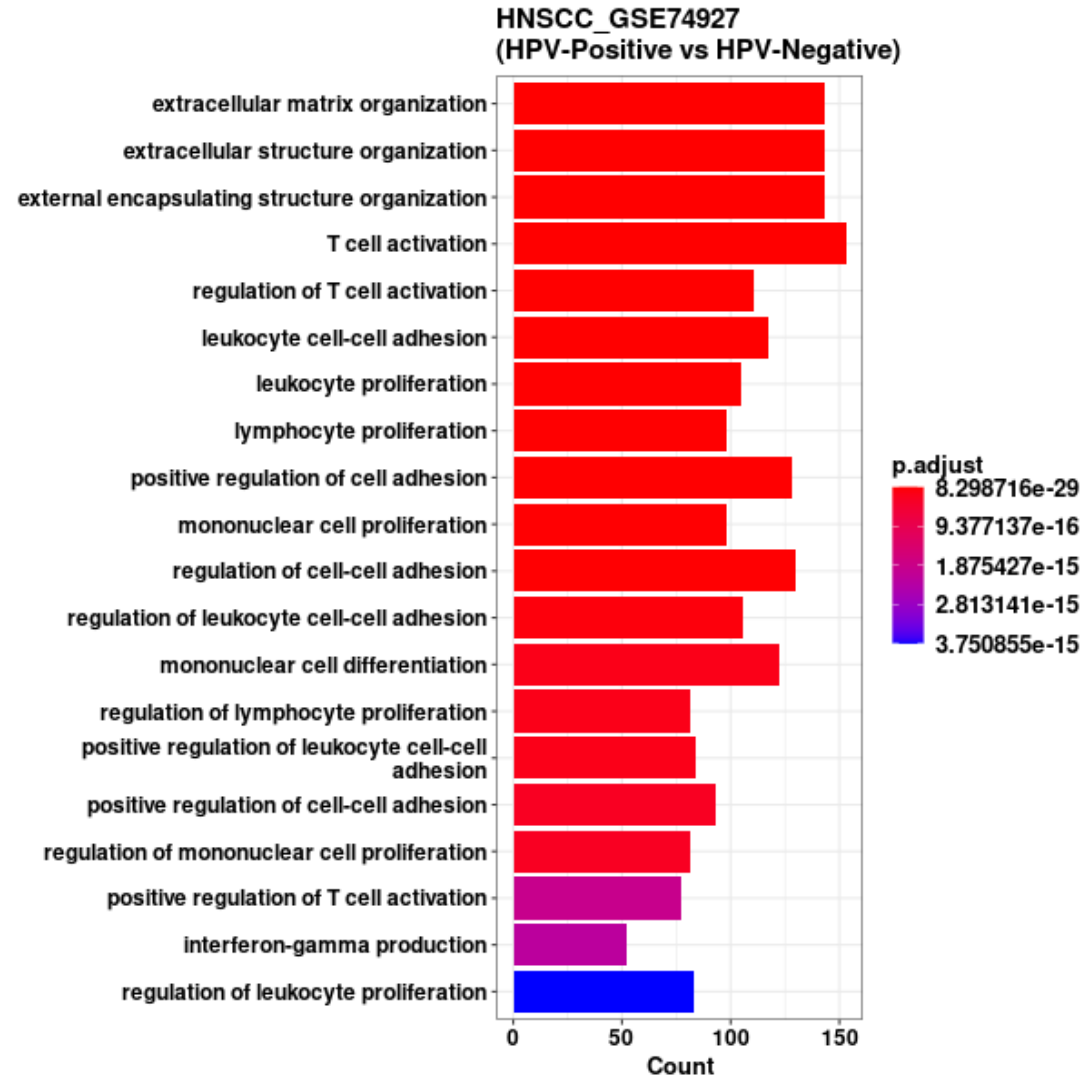
- 7种可视化图: 条形图, 散点图, 富集图, 山脊图, GSEA图, KEGG通路图, 热图

- 自定义分析参数及绘图参数

The screenshot shows the HPVTIMER web application interface. The top navigation bar is dark purple with the HPVTIMER logo and a hamburger menu icon. A left sidebar contains navigation links: Introduction, DE analysis, Correlation, Immune infiltration, Pathway analysis, Pathway enrichment, Pathview, and ssGSEA. The main content area is titled "Pathway Enrichment" and features two tabs: "Over Representation Analysis(ORA)" and "Gene Set Enrichment Analysis(GSEA)". The GSEA tab is active. Below the tabs, there are input fields for "Search, select a dataset:" (set to HNSCC\_GSE74927 (n=36)) and "Pick genesets for enrichment:" (set to GO(Gene Ontology gene sets)). To the right, there are radio buttons for "Choose the pathways to display:" (Top20 is selected, Customize is unselected) and a "Visualize" button. A copyright notice "Copyright © 2023. All rights reserved." is at the bottom.

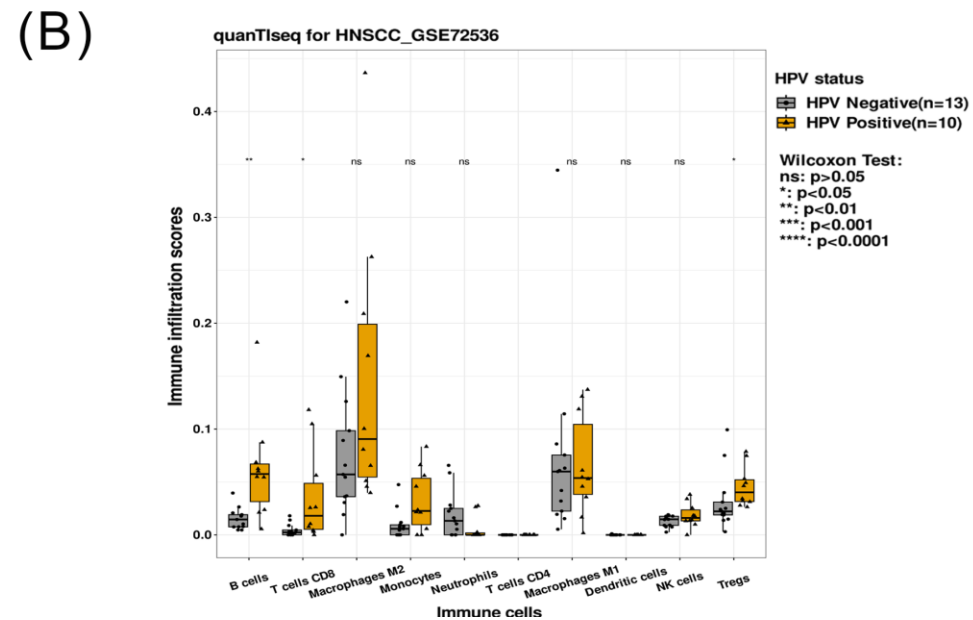
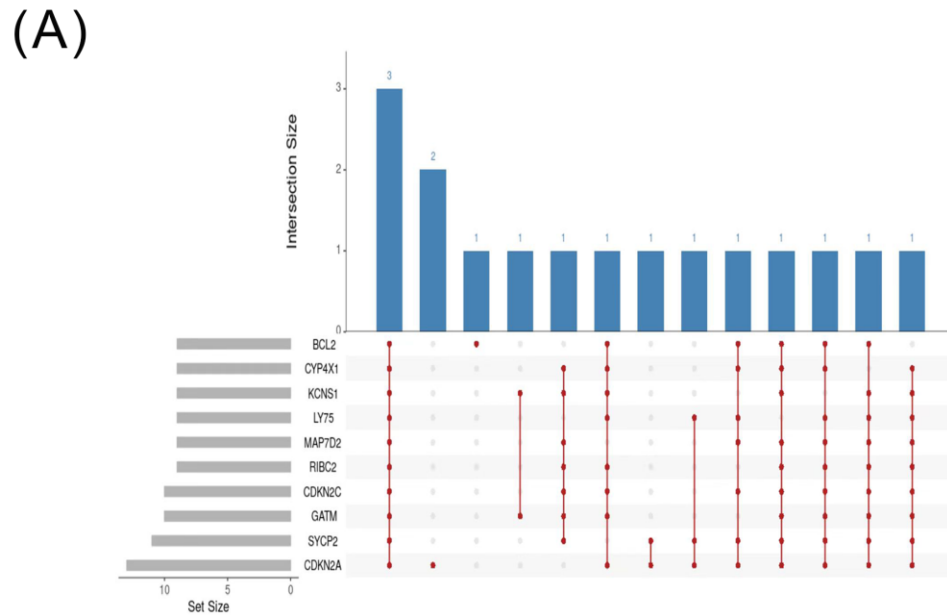
# 结果

## ● 通路分析 (Pathway analysis)



# 结果

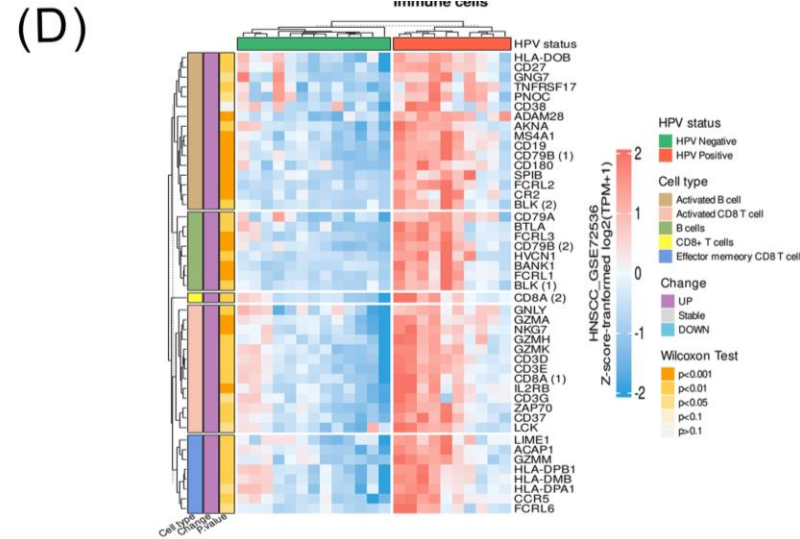
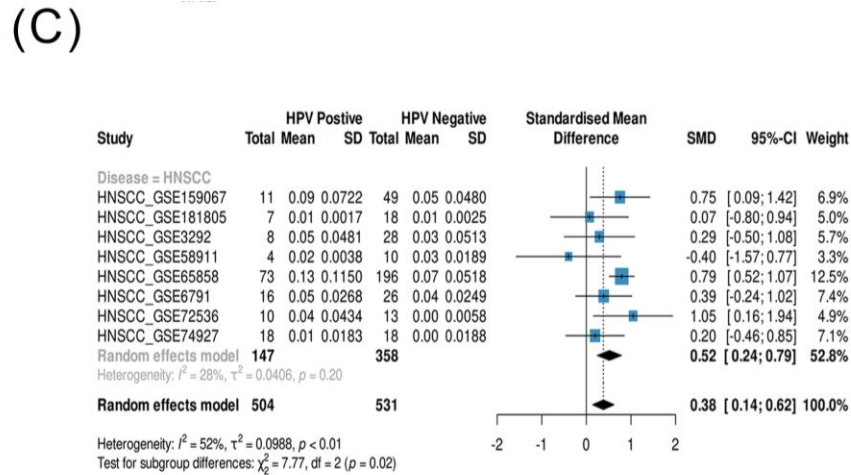
- 实例展示：CDKN2A参与调控HPV+头颈鳞癌肿瘤免疫微环境
- 涉及模块：DE分析模块，相关性分析模块，免疫浸润模块，通路分析模块
- 涉及的子模块：DE分析-Immune Cells，相关性分析-Co-expression, Scatter plot, Multigenes, Meta analysis，免疫浸润分析-Immune Cells, Meta analysis，通路分析-Pathway enrichment, ssGSEA



CDKN2A在13个数据集中的HPV阳性样本内显著上调。  
在HPV阳性样本和HPV阴性样本之间，CD8+ T细胞免疫浸润评分存在明显差异。

# 结果

## ● 实例展示：CDKN2A参与调控HPV+头颈鳞癌肿瘤免疫微环境



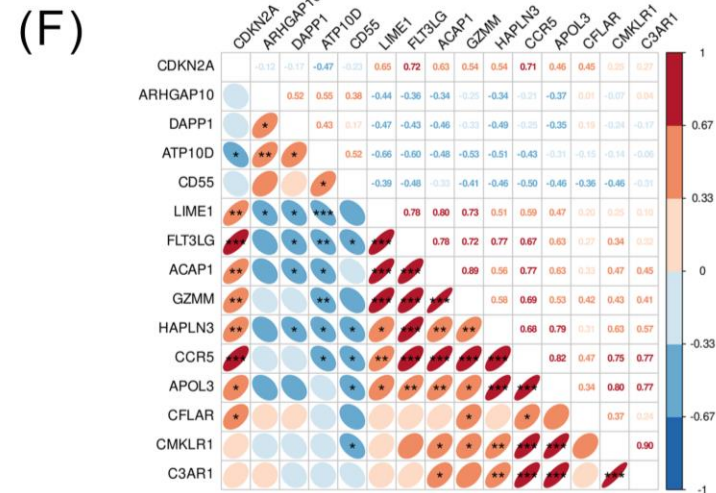
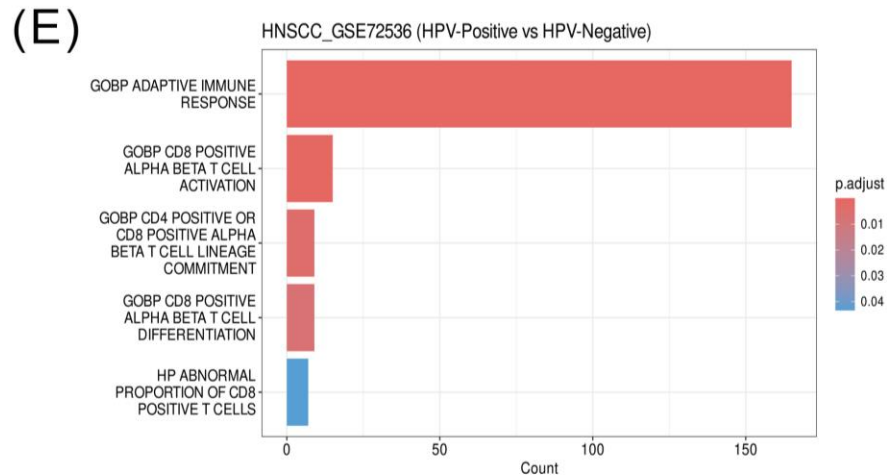
- CD8+ T细胞相关的基因在HPV阳性样本与阴性样本间有显著的表达差异 ( $p < 0.05$ ,  $|\log_2FC| > 1.0$ )

- 多个CD8+ T细胞相关通路 (CD8+  $\alpha$ -beta T细胞活化等) 在

HNSCC\_GSE72536中显著富集 ( $p.adjust < 0.01$ )

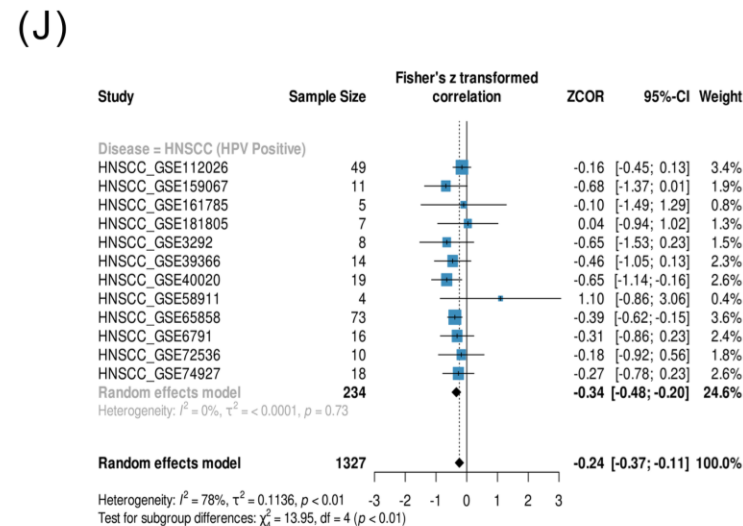
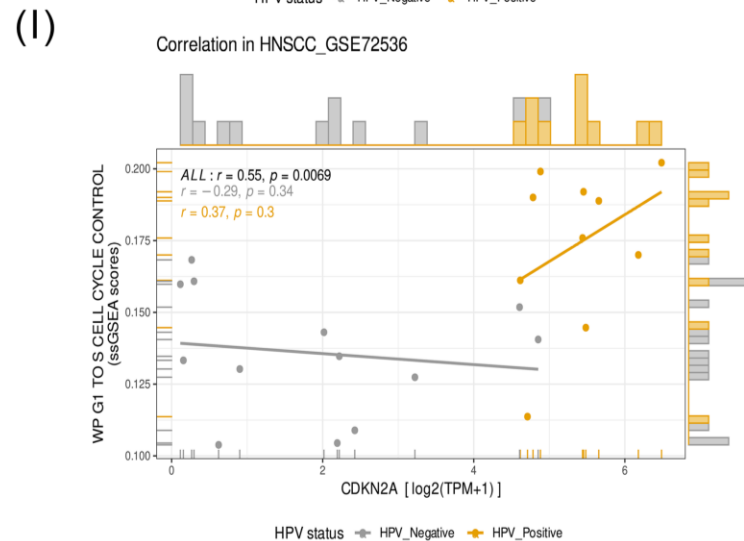
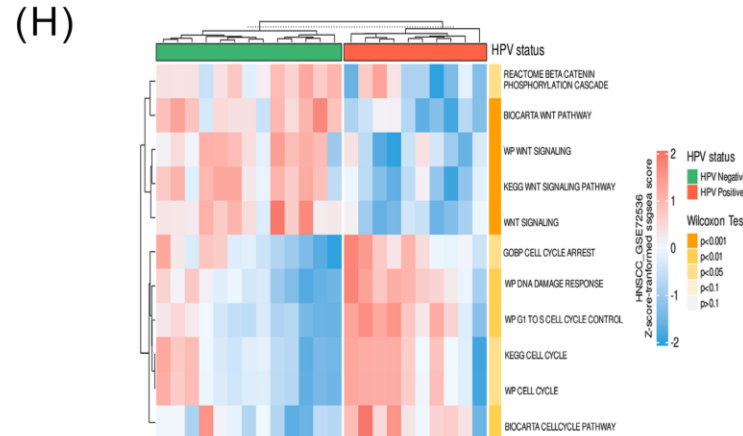
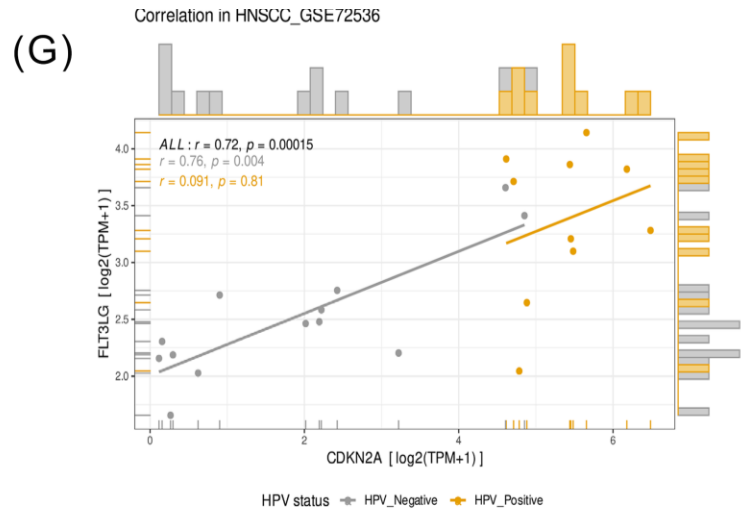
- 多个CD8+ T细胞相关通路 (CD8+  $\alpha$ -beta T细胞活化等) 在

HNSCC\_GSE72536中显著富集 ( $p.adjust < 0.01$ )



# 结果

## ● 实例展示：CDKN2A参与调控HPV+头颈鳞癌肿瘤免疫微环境



- 在HNSCC\_GSE72536中，细胞周期相关通路和DNA损伤应答通路的ssGSEA得分在HPV阳性样本中明显上调（p value < 0.05），而Wnt/ $\beta$ -catenin相关通路的ssGSEA得分在HPV阳性样本中显著下调（p value < 0.05）。

- CDKN2A与细胞周期相关通路呈显著正相关，但与Wnt/ $\beta$ -catenin相关通路呈显著负相关。

# 总结

- HPVTIMER作为一个综合分析平台，整合了基因表达总库（GEO）内现有的8种HPV相关肿瘤共65个转录组数据集2290个样本超过10000个基因的表达数据。
- 内置的4个分析模块，即差异表达分析模块、相关性分析模块、免疫浸润分析模块和通路分析模块，帮助用户纵向系统分析和横向比较数据，有助于用户探索HPV相关肿瘤的免疫微环境，发现潜在的免疫调节机制和免疫治疗靶点。
- HPVTIMER的源代码已在<https://github.com/SMULiuLY/HPVTIMER/>公开
- 在线访问: [www.hpvtimer.com](http://www.hpvtimer.com)
- 联系: [luopeng@smu.edu.cn](mailto:luopeng@smu.edu.cn)

Liyang Liu, Yanan Xie, Hong Yang, Anqi Lin, Minjun Dong, Haitao Wang, Cangang Zhang, Zaoqu Liu, Quan Cheng, Jian Zhang, Shuofeng Yuan, Peng Luo. 2023. HPVTIMER: A Shiny web application for tumor immune estimation in human papillomavirus-associated cancers. *iMeta* 1: e1. <https://doi.org/10.1002/imt2.130>



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