

15-16 February 2021

COMETH Training course

From omics data

to tumor heterogeneity quantification

EIT Health is supported by the EIT,
a body of the European Union



The program

DAY2



9:00 -10:00 pm LECTURE

9:00-10:00 pm Visualization and interpretation



10:00 -12:00 pm Practical work

Medical contributors

Using COMETH web app on real datasets: small projects

Computational contributors

Submit novel computational methods on codabench



Lunch Break



2:00-4:00 pm Practical work

2:00-2:30 pm Debriefing with slides from teams



Medical & Computational contributors

2:30-4.00 pm Focus on biological interpretation



4:00-4:45 pm PRESENTATIONS

2:00-2:45 pm Results presentation & discussion



4:45 -5:00 pm CONCLUSION



In practical during the COMETH training

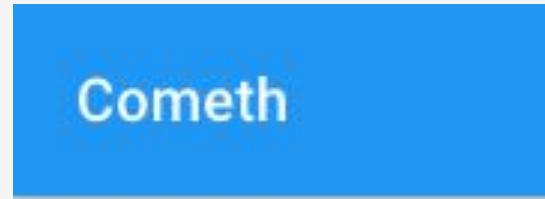


Edit Participants Submissions Dumps Migrate
ORGANIZED BY: Magrichardtest
CURRENT PHASE ENDS: 15 Mars 2021 à 01:00 UTC+1
CURRENT SERVER TIME: 9 Février 2021 à 10:26 UTC+1
Secret url: https://www.codabench.org/competitions/237/?secret_key=b164d1c1-07ca-4d0c-b55f-99e68af3a343



Computational group DAY 1-2

Learn how to contribute to the codabench benchmark using a toy data challenge



Medical group DAY 1-2

Learn how to use the user-friendly COMETH web application to run methods on toy TCGA datasets



The screenshot shows a Shiny web application interface. At the top left, there is a blue button with the word "Shiny" in white. To its right is a histogram with the title "Histogram of waiting times". The x-axis is labeled "Waiting time to next operation (in mins)" and ranges from 0 to 100. The y-axis is labeled "Number of times" and ranges from 0 to 10. The histogram bars are blue.

DAY 2

Learn how to biologically interpret the results of the methods

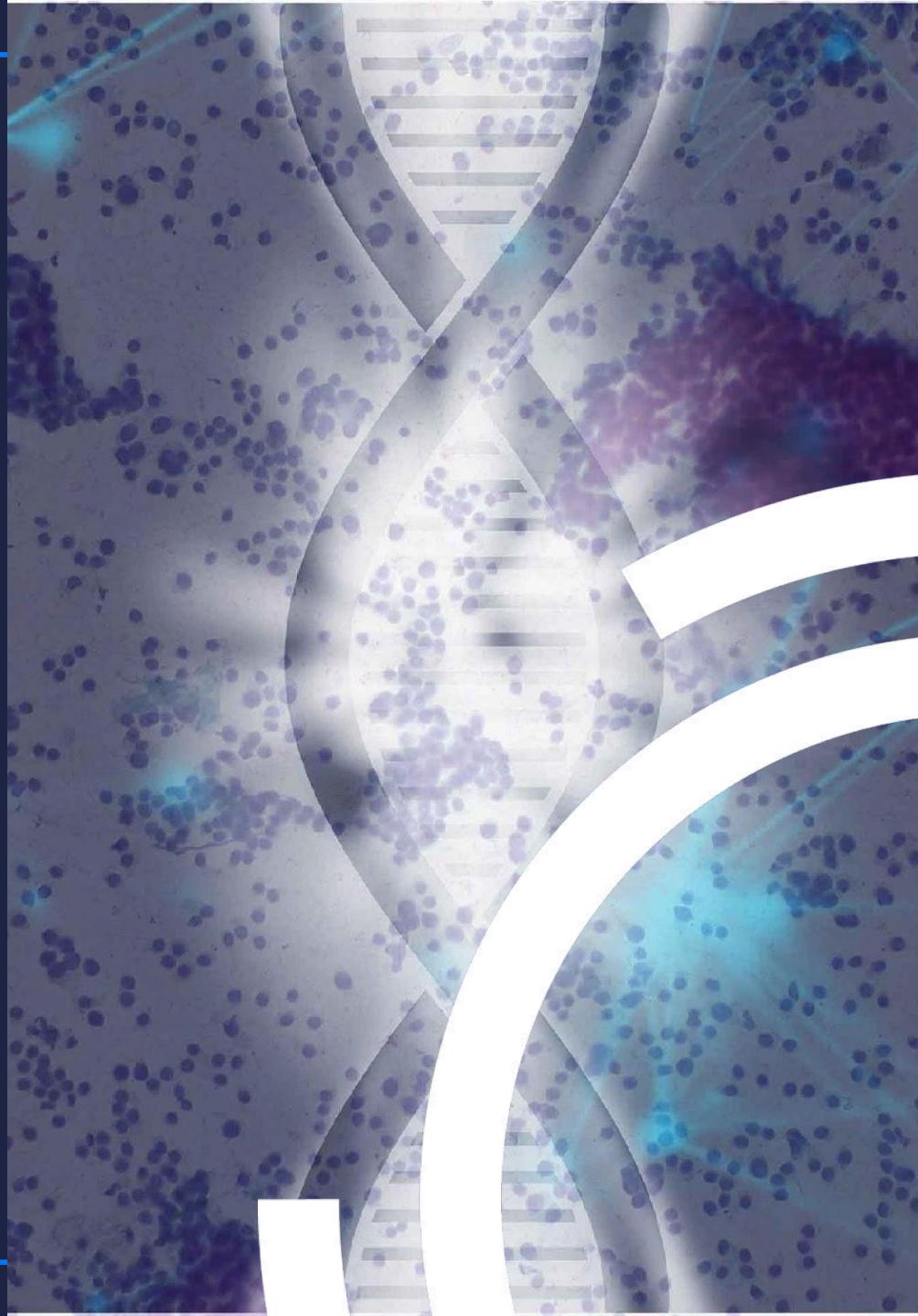




16 February 2021

Biological interpretation

Yuna Blum and Ashwini Sharma



compExplore Shiny app



Help you in the analysis, interpretation and visualization of the results

[compExplore](#) [About](#) [CSV-converter](#) [Number of CellTypes](#) [Components enrichment](#) [Proportion vizualisation](#)

compExplore

Different modules

compExplore - Components explorer is a visualization tool to guide the user in the analysis and interpretation of the results from *Supervised* and *Unsupervised* gene expression deconvolution algorithms.

The diagram illustrates the decomposition of a complex tissue into cell types using gene expression matrices. On the left, a box labeled "Complex tissue with multiple cell types" contains several colored circles representing different cell types. An arrow labeled "Bulk RNAseq" points from this box to a heatmap labeled "Gene expression matrix ($k \times m$)". This matrix is shown as a grid of blue and yellow squares, representing genes on the rows and samples on the columns. To the right of the matrix is an equals sign (=). To the right of the equals sign are three matrices: "Gene signature matrix ($k \times n$)" (a grid of colored squares), "Cell proportion matrix ($n \times m$)" (a grid of colored squares), and "Samples" (a row of colored circles). Arrows point from the text labels above each matrix to their respective components. A legend at the top left shows "Normal Tissue or Tumor microenvironment" with a blue circle, "Cell type" with a green circle, and "mRNA" with a red wavy line.

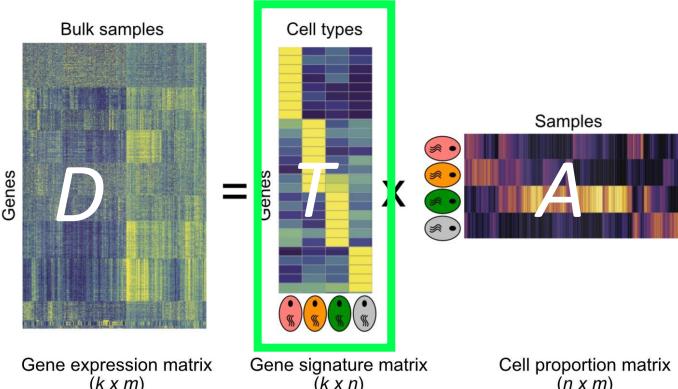
Terminology

1. Gene expression matrix - it is a $k \times m$ matrix with k rows of genes and m columns of samples. Each data point in this matrix represents the expression of a given gene in a given sample
2. Gene signature matrix - it is a $k \times n$ matrix with n rows of genes and m columns of cell fraction. Each data point in this matrix represents the contribution of a gene towards a cell type
3. Cell proportion matrix - it is a $n \times m$ matrix with n rows of cell types and m columns of samples. Each data point in this matrix represents the proportion of a given cell type in a given sample

<https://app.gebican.fr/compExplore/>

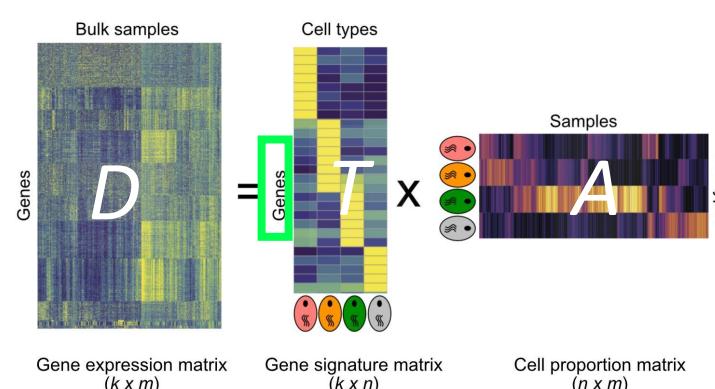
Different type of computational methods

Supervised



T matrix known

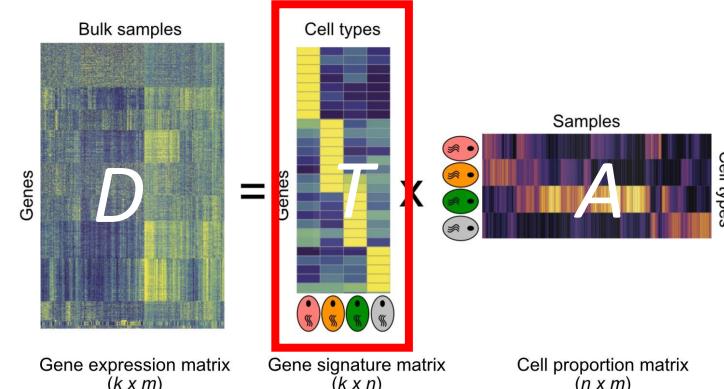
Semi-supervised



Gene markers known

Cibersort (MT8), EPIC (MT9), quantiseq (MT11)

Unsupervised



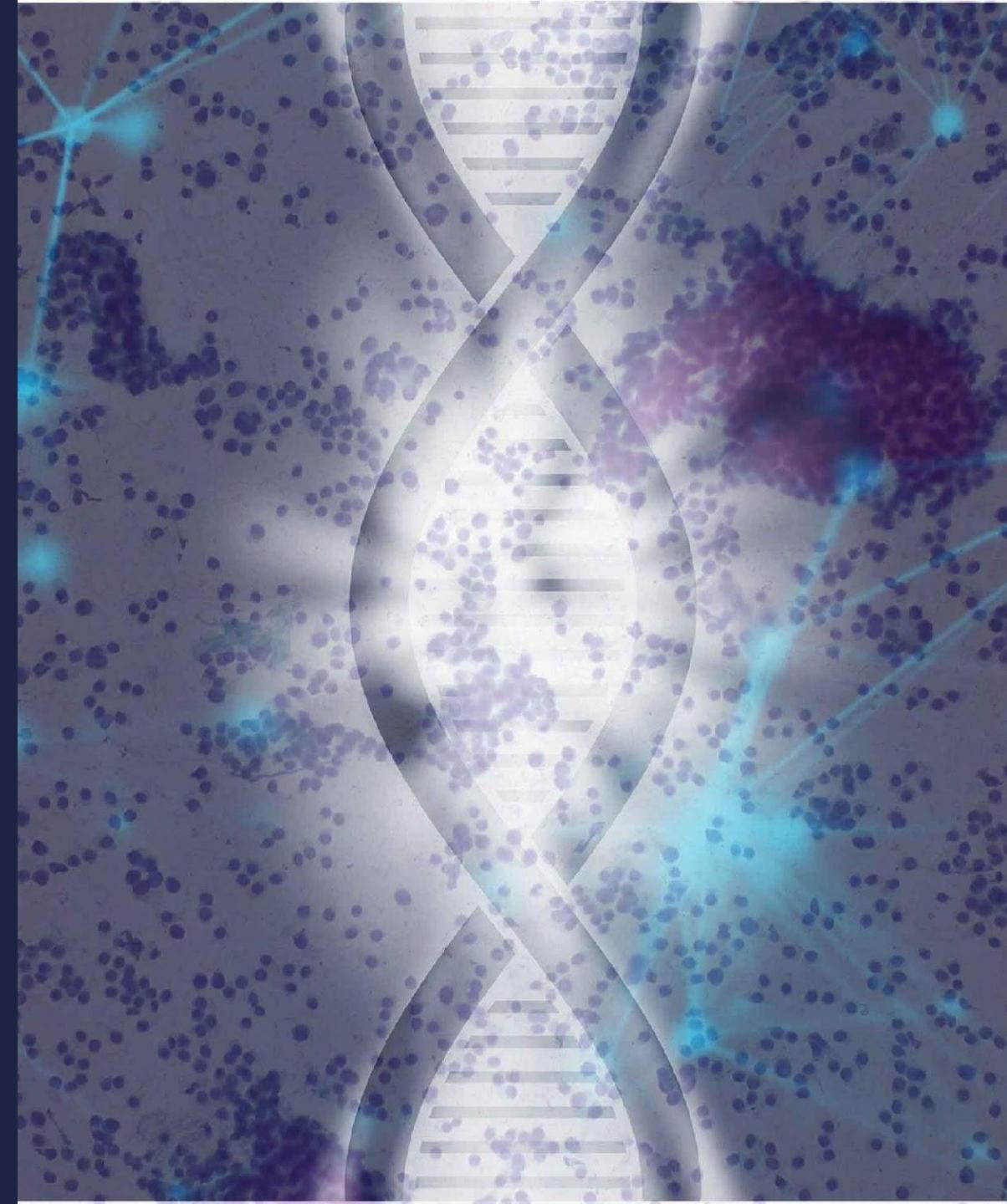
T matrix unknown

Number of component to consider (#cell types)?

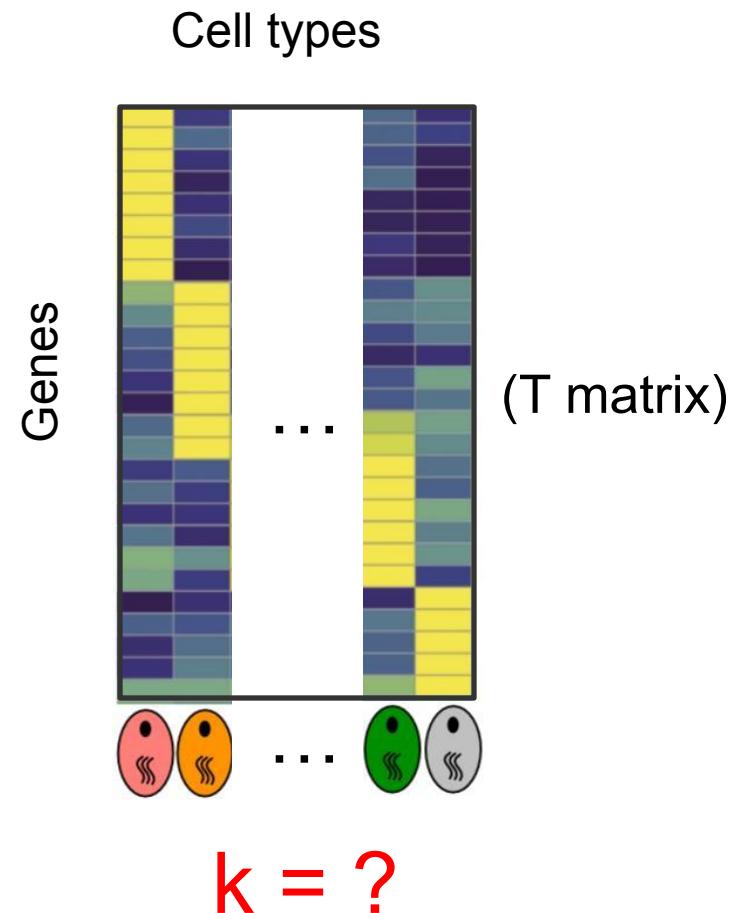
Interpretation of the components

ICA with fs (MT1_ICA_fs,), NMF with fs (MT2_NMF_fs ,), Edec method (MT3_edec ,), ICA without fs (MT14_ICA), NMF without fs (MT19_NMF)

Unsupervised methods: finding the number of k of cell types



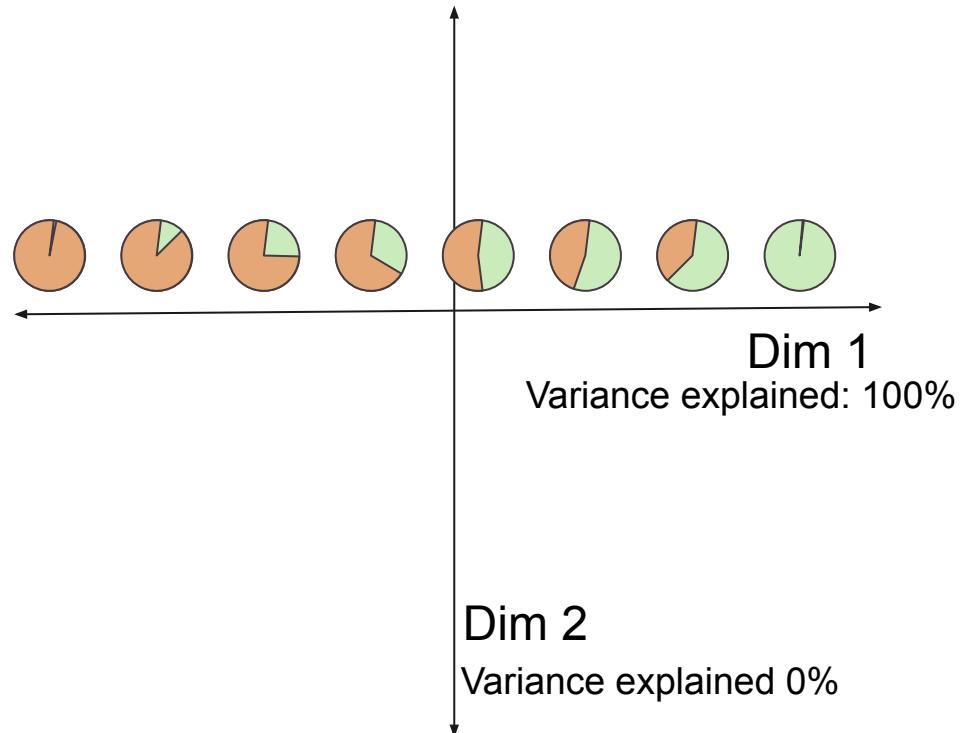
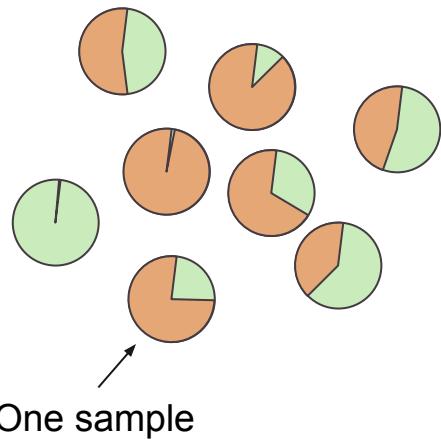
Finding the number of cell types k



Finding the number of cell types k

Principal Component Analysis (PCA)

Samples
mixtures of 2 cell types

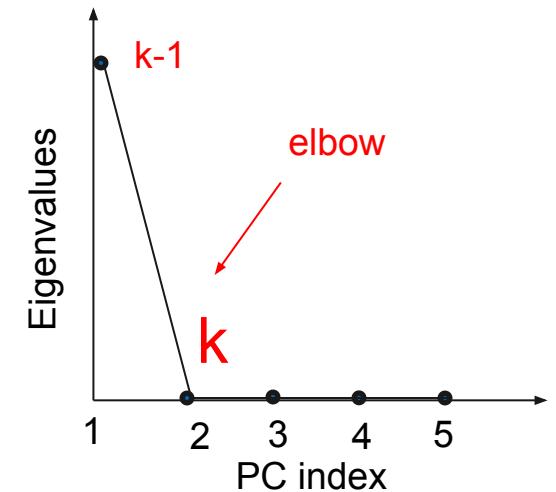


Reminder

Find the axes that maximized the explained variance (inertia)

Principal components are orthogonal

Plot of eigenvalues (=scree plot)



Eigenvalues represent the variance explained

Cattel's rule: $k = \text{PCs} + 1$

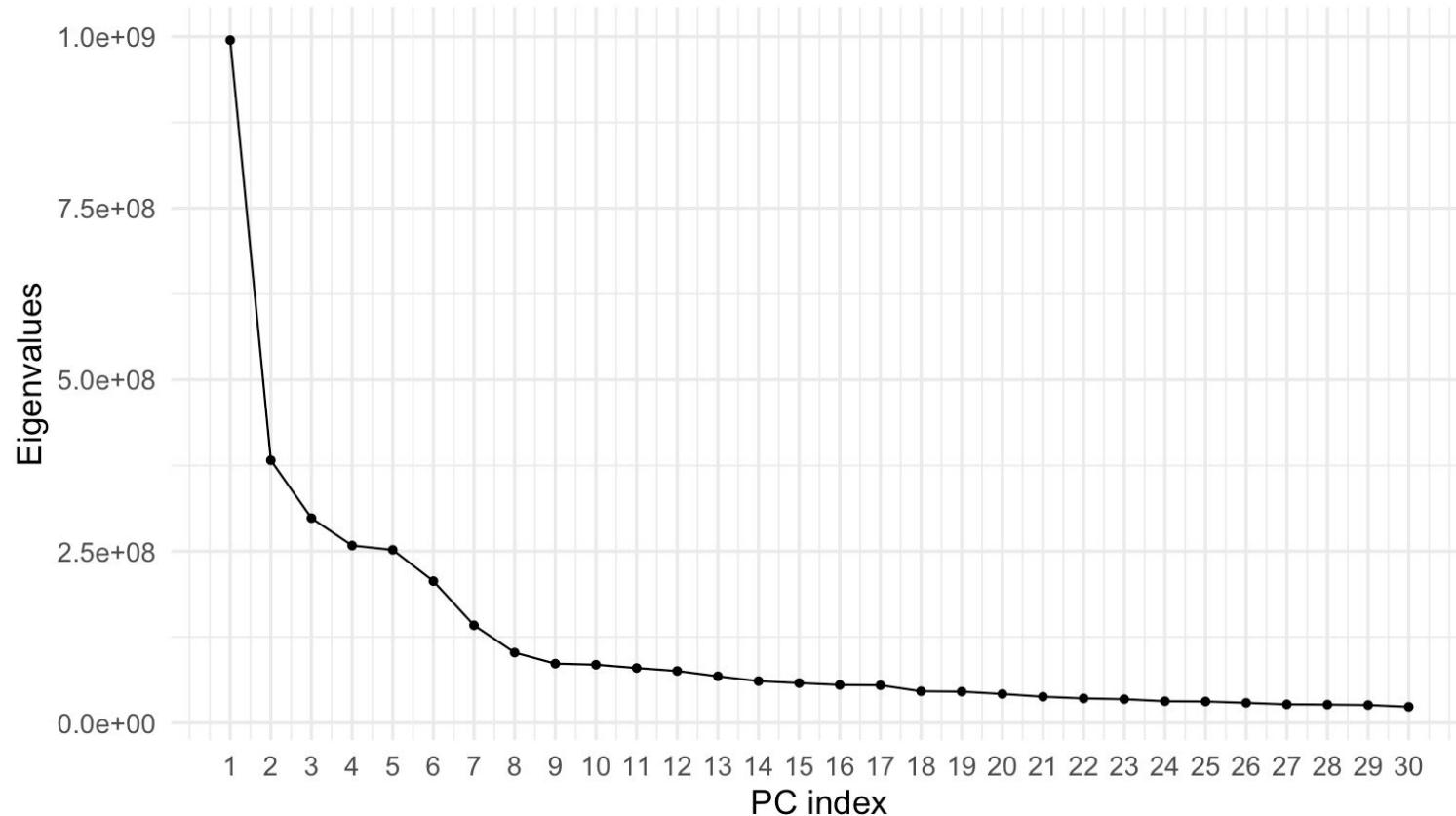
Number of relevant PCs

Finding the number of cell types k

Real life

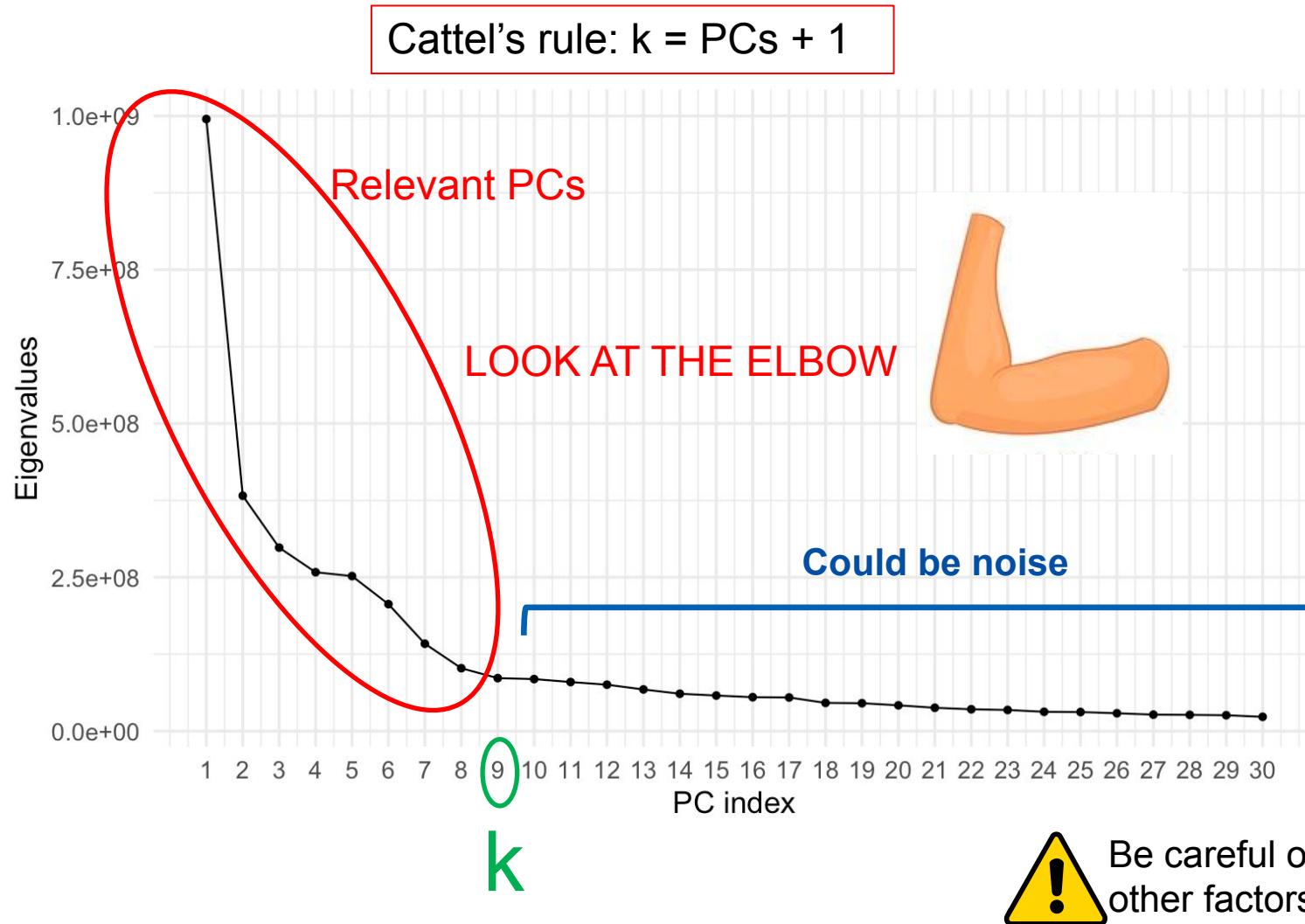


Cattel's rule: $k = \text{PCs} + 1$

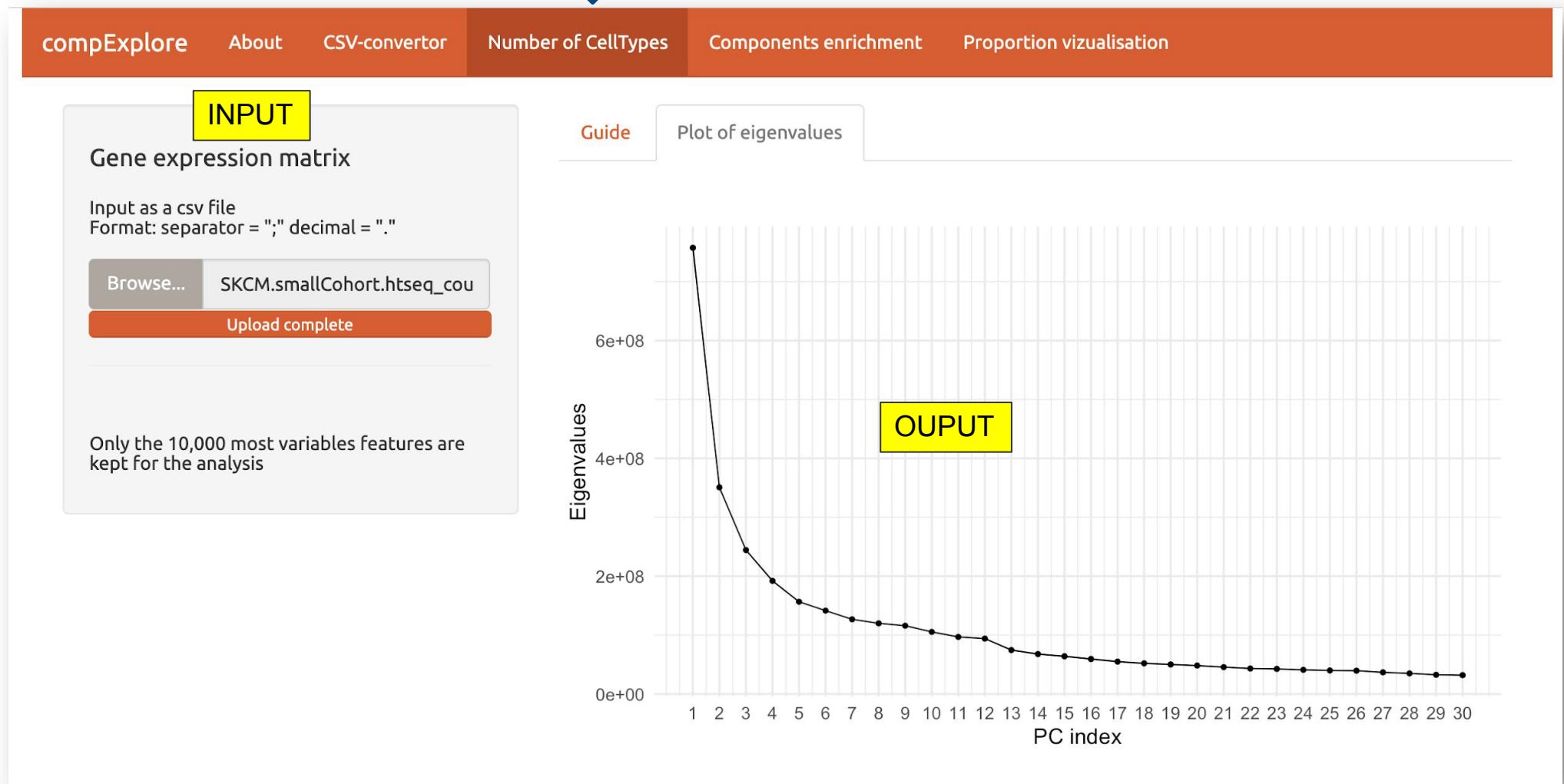


Finding the number of cell types k

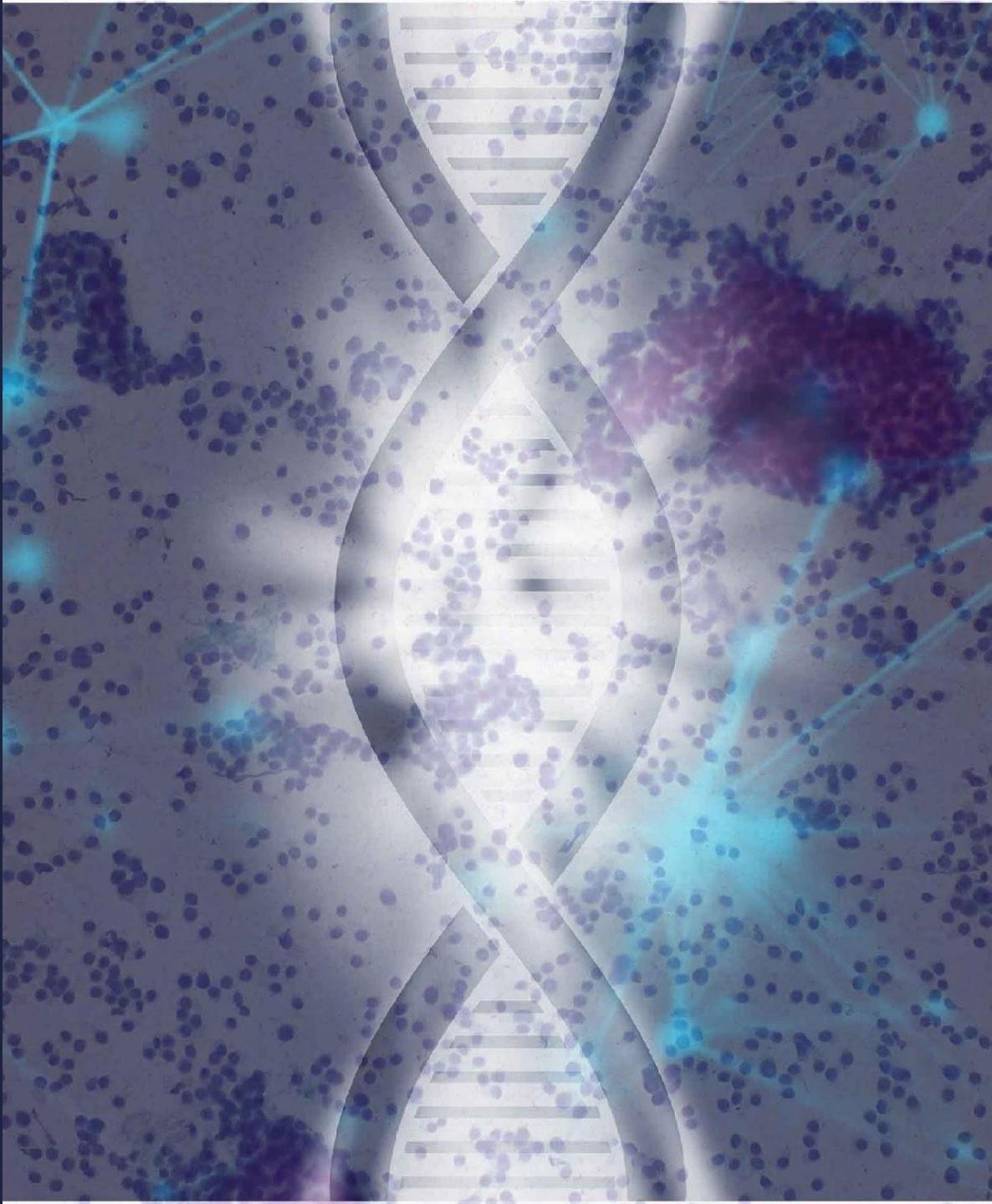
Real life



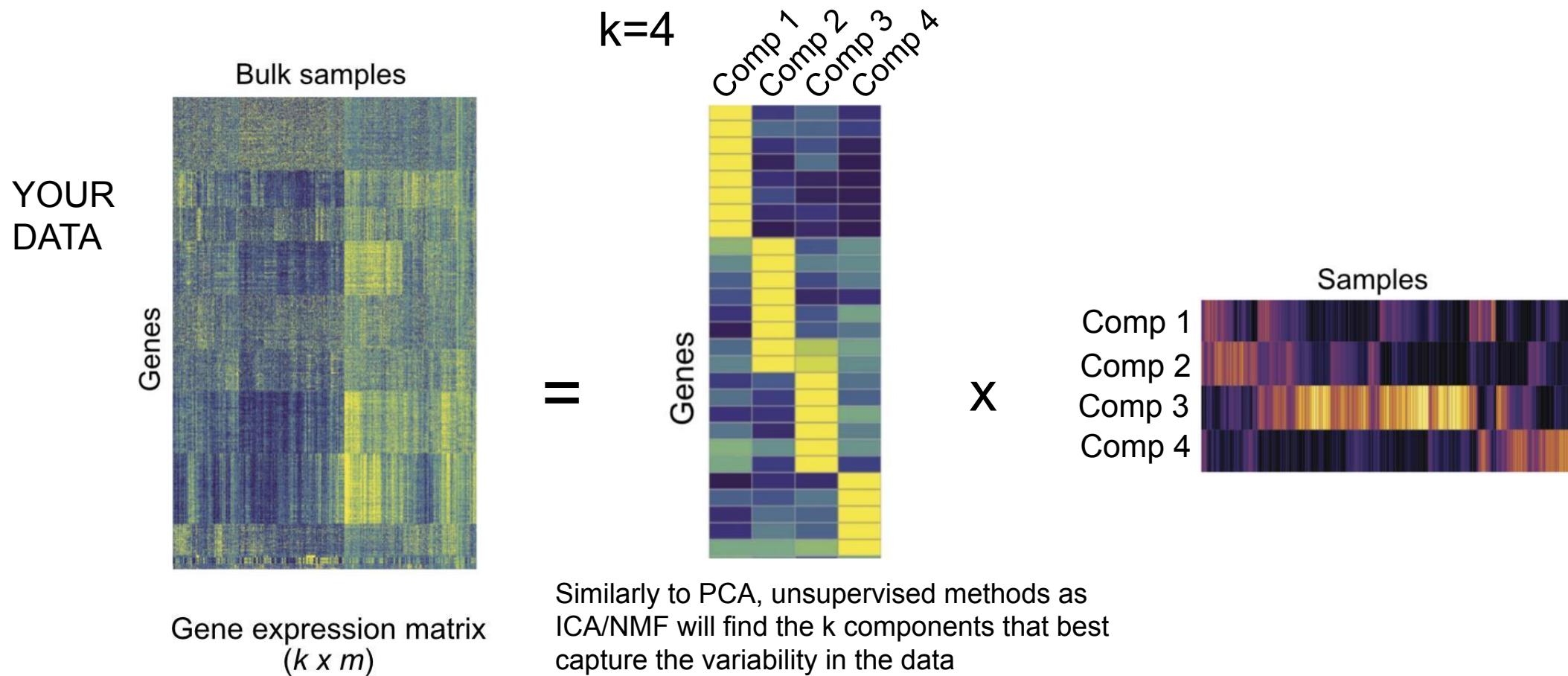
compExplore Shiny app



Unsupervised methods: Interpret the components identified

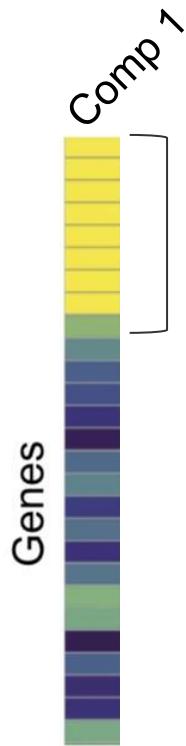


Interpret the components identified

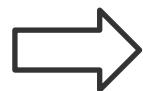


To which cell type(s) corresponds each of the components identified by unsupervised methods?

Interpret the components identified



Genes with high scores
on the component



Markers of a particular cell
types?

Use of *CellMatch* Database

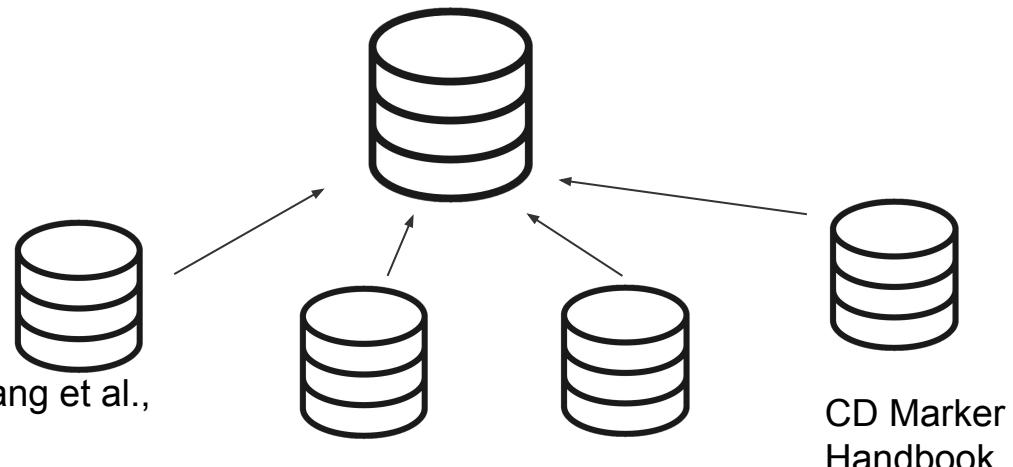
(Shao et al iScience, 2020, tool scCATCH)



Interpret the components identified

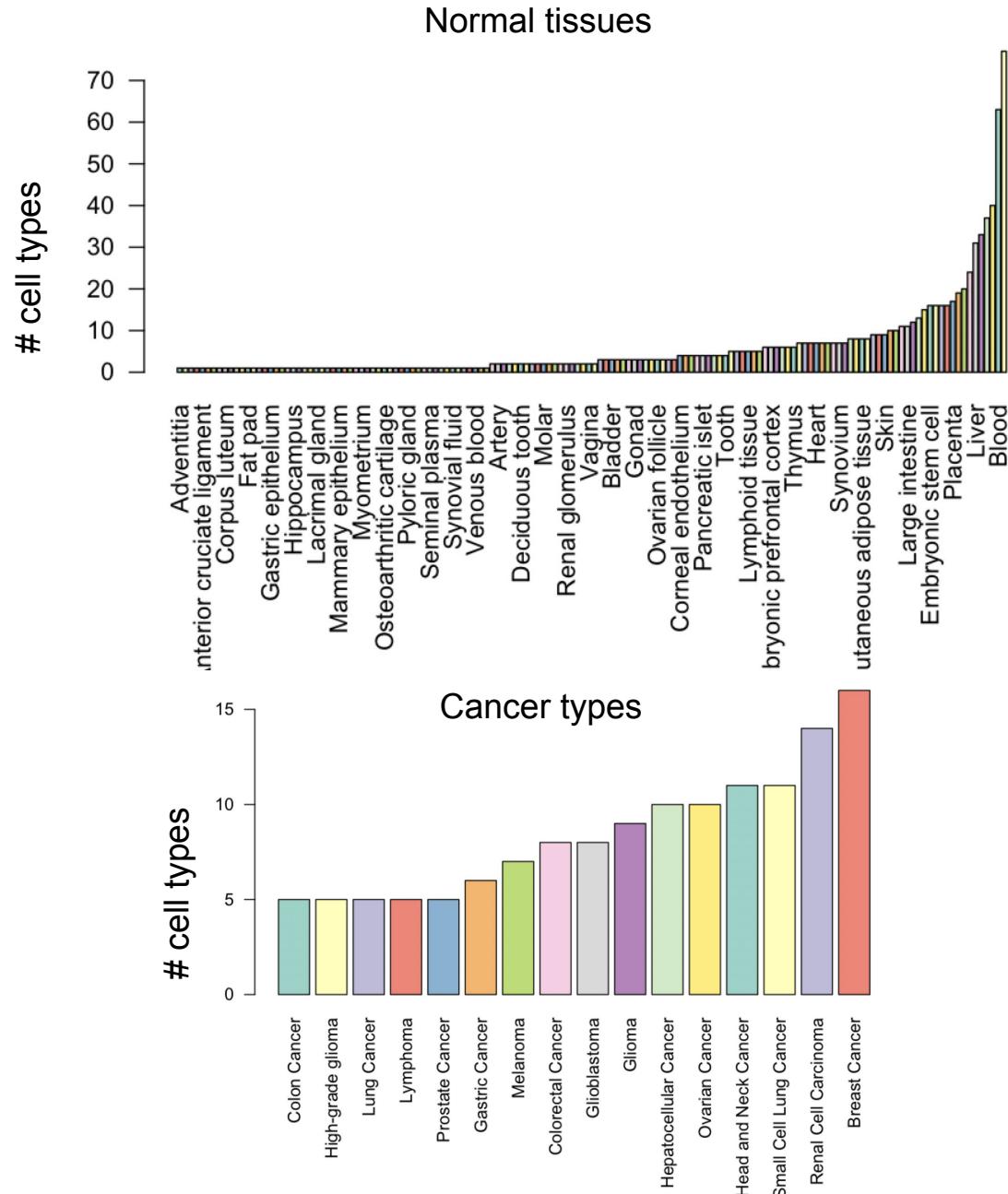
Use of *CellMatch* Database

(Shao et al iScience, 2020, tool scCATCH)

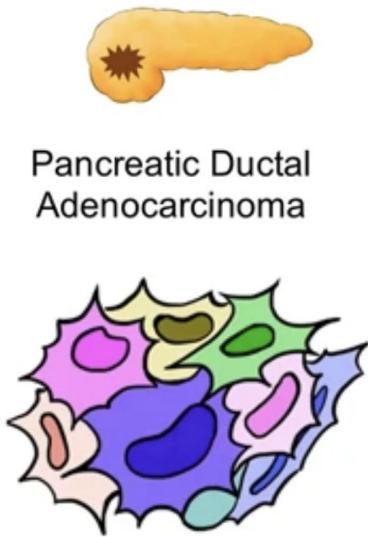


- **33** cancer types + normal
- **150** tissues
- **412** cell types
- **12312** gene markers

Filtering human gene markers and cancer types with at least 5 gene markers



Interpret the components identified

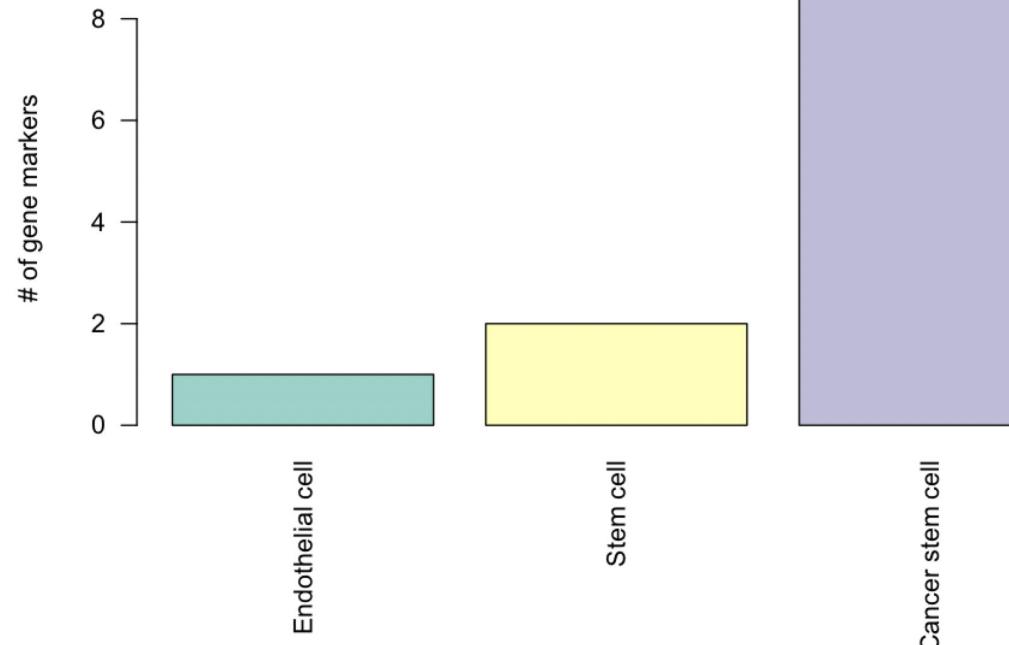


Cell Type
Ductal cell 1
Ductal cell 2
Acinar cell
Endocrine cell
Endothelial cell
Fibroblast
Stellate cell
Macrophage
T cell
B cell

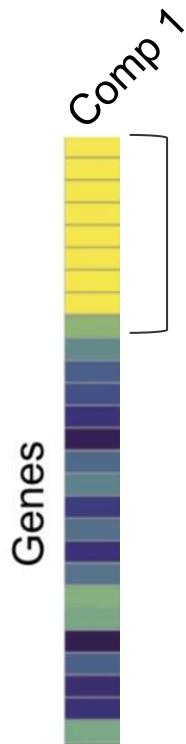
Peng et al 2019 Nature

CellMatch Database

PDAC cell types



Interpret the components identified



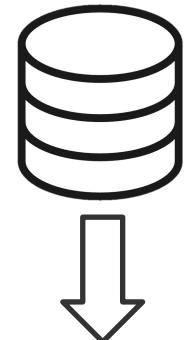
Genes with high scores
on the component



Markers of a particular cell
types?

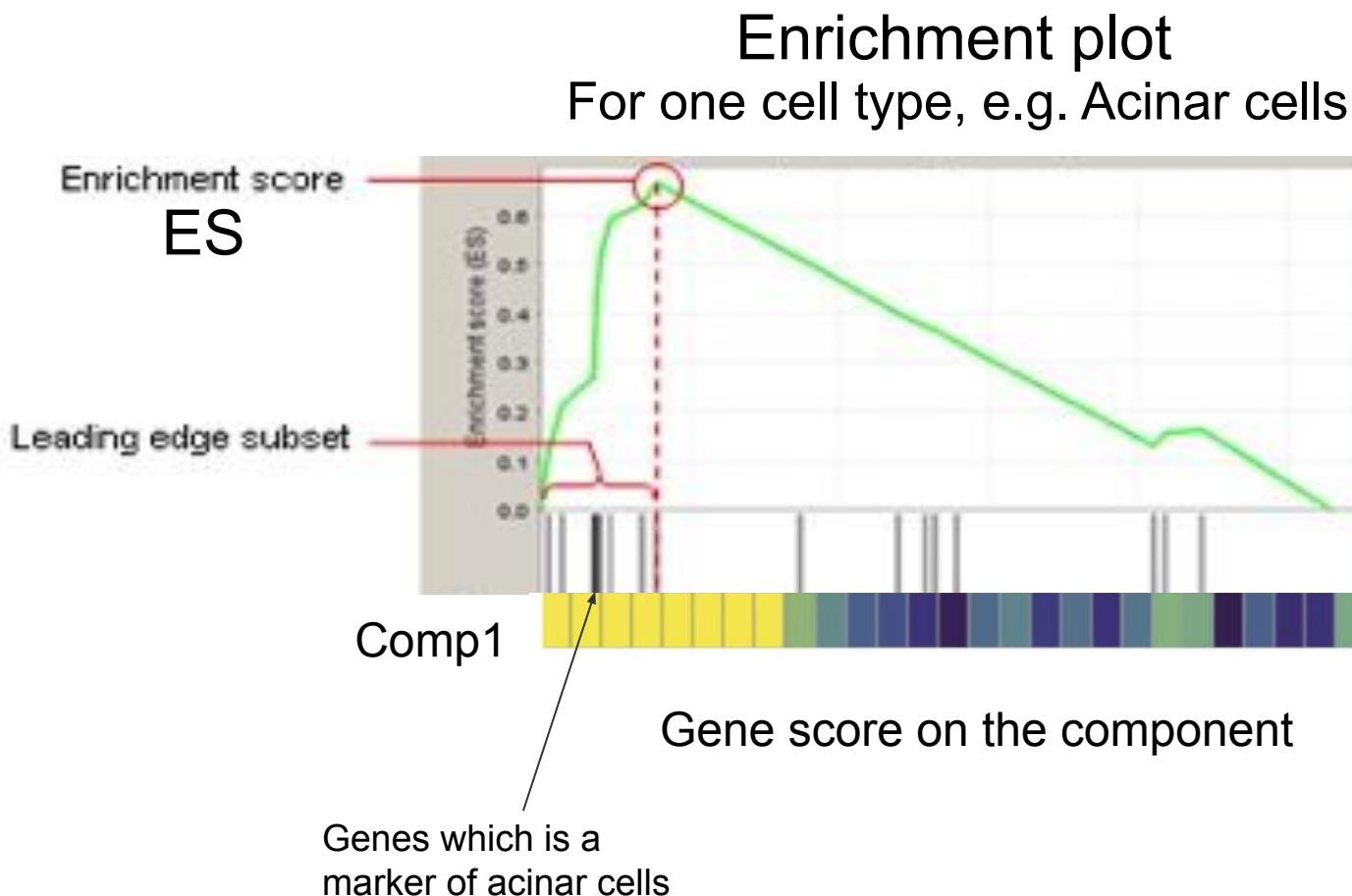
Use of *CellMatch* Database

(Shao et al iScience, 2020, tool scCATCH)



Gene Set Enrichment
Analysis (GSEA)

Gene Set Enrichment Analysis (use of the fgsea R package)



- 1- Order the list of genes (test statistic, p-value, here component scores...)
- 2- Calculation of the Enrichment Score (ES)

The algorithm scans the list: the score increases when the gene is part of the set (=cell type) and decreases otherwise. The increase and decrease values is weighted by the gene rank (for a gene set overexpressed, the increase will be higher at the beginning of the list).
The ES corresponds to the max score (absolute value).

- 3- Comparison of ES to a distribution of ES obtained on random data (gene permutations) . → Calculation of a p-value

compExplore Shiny app



INPUT

Gene signature matrix

Input as a csv file
Format: separator = ";" decimal = ","

The Gene signature matrix corresponds to the output results_T_1.csv in the comet web-app which is already in the requested format (separator = ";" decimal = ",").

Deconvolution method

ICA-based
 NMF-based

Cancer type

Download top markers

Top100 gene markers for each component

Guide **Enrichment analysis** **OUTPUT**

Gene set enrichment analysis results using CellMatch DB

V1

pathway	ES	-log10(pval)
Non_Small_Cell_Lung_Cancer.Fibroblast	0.975	4.5
Normal.Fibroblast	0.950	3.8
Colorectal_Cancer.CancerAssociated_Fibroblast	0.935	3.5
Head_and_Neck_Cancer.Fibroblast	0.925	3.2
Oligodendroglioma.Microglial_Cell	0.915	3.0
Glioma.Astrocyte	0.905	2.8
B_Cell.Lymphoma.B_Cell	0.900	2.6
Normal.Circulating_Fetal_Cell	0.900	2.4
Melanoma.CancerAssociated_Fibroblast	0.900	2.2
Normal.Stromal_Cell	0.900	2.0

V2

pathway	ES	-log10(pval)
Normal.Primitive_Vesicle_Cell	0.80	3.5
Head_and_Neck_Cancer.Mycocyte	0.75	3.2
Renal_Cell_Carcinoma.Erythroblast	0.70	3.0
Melanoma.B_Cell	0.65	2.8
Normal.Photoreceptor_Cell	0.60	2.6
Normal.Enterocrinology_Cell	0.55	2.4
Normal.Streak_Cell	0.50	2.2
Normal.Lake_Et_Al.science.in2	0.45	2.0

V3

pathway	ES	-log10(pval)
Normal.1Cell_Stage_Cell_Blastomere	0.975	4.5
Normal.Secretory_Cell	0.950	3.8
Ovarian_Cancer.Cancer_Cell	0.935	3.5
Normal.Alpha_Cell	0.925	3.2
Astrocytoma.Astrocyte	0.915	3.0
Melanoma.Macrophage	0.905	2.8
Colon_Cancer.Stem_Cell	0.900	2.6
Glioma.Astrocyte	0.900	2.4
Normal.Mast_Cell	0.900	2.2
Renal_Cell_Carcinoma.Neutrophil	0.900	2.0

V4

pathway	ES	-log10(pval)
Normal.Idiopathic_Pulmonary_Fibrosis_Cell	0.95	4.5
Melanoma.CancerAssociated_Fibroblast	0.90	3.8
Head_and_Neck_Cancer.Fibroblast	0.85	3.5
Colorectal_Cancer.CancerAssociated_Fibroblast	0.80	3.2
Non_Small_Cell_Lung_Cancer.Myeloid_Cell	0.75	3.0
Normal.Bile_Duct_Cell	0.70	2.8
Normal.Mesangial_Cell	0.65	2.6
Head_and_Neck_Cancer.Cancer_Cell	0.60	2.4

V5

pathway	ES	-log10(pval)
Colorectal_Cancer.CancerAssociated_Fibroblast	0.98	6.0
Non_Small_Cell_Lung_Cancer.Fibroblast	0.975	5.8
Normal.Myofibroblast	0.970	5.5
Ovarian_Cancer.Mesenchymal_Cell	0.965	5.3
Normal.Mesangial_Cell	0.960	5.0
Normal.Bile_Duct_Cell	0.955	4.8
Head_and_Neck_Cancer.Fibroblast	0.950	4.5
Normal.Fibroblast	0.945	4.2
Normal.Idiopathic_Pulmonary_Fibrosis_Cell	0.940	4.0
Normal.Pneumocyte	0.940	3.8

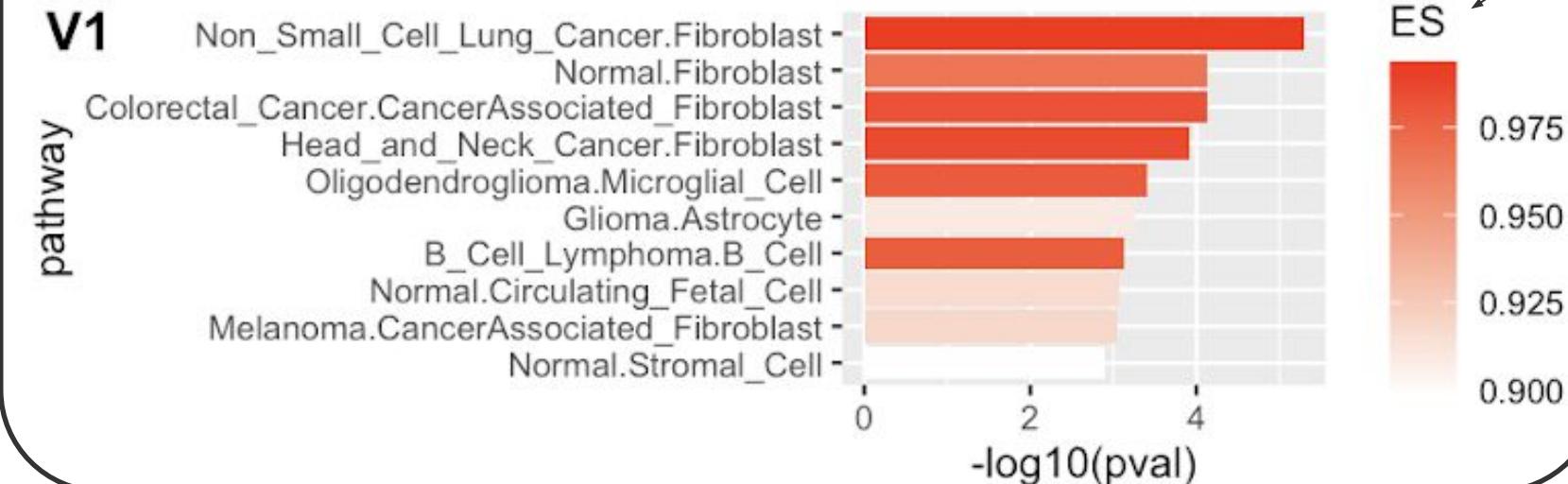
compExplore Shiny app



Example for component 1

(LUAD dataset, ICA method, k=5)

Gene set enrichment analysis results using CellMatch DB

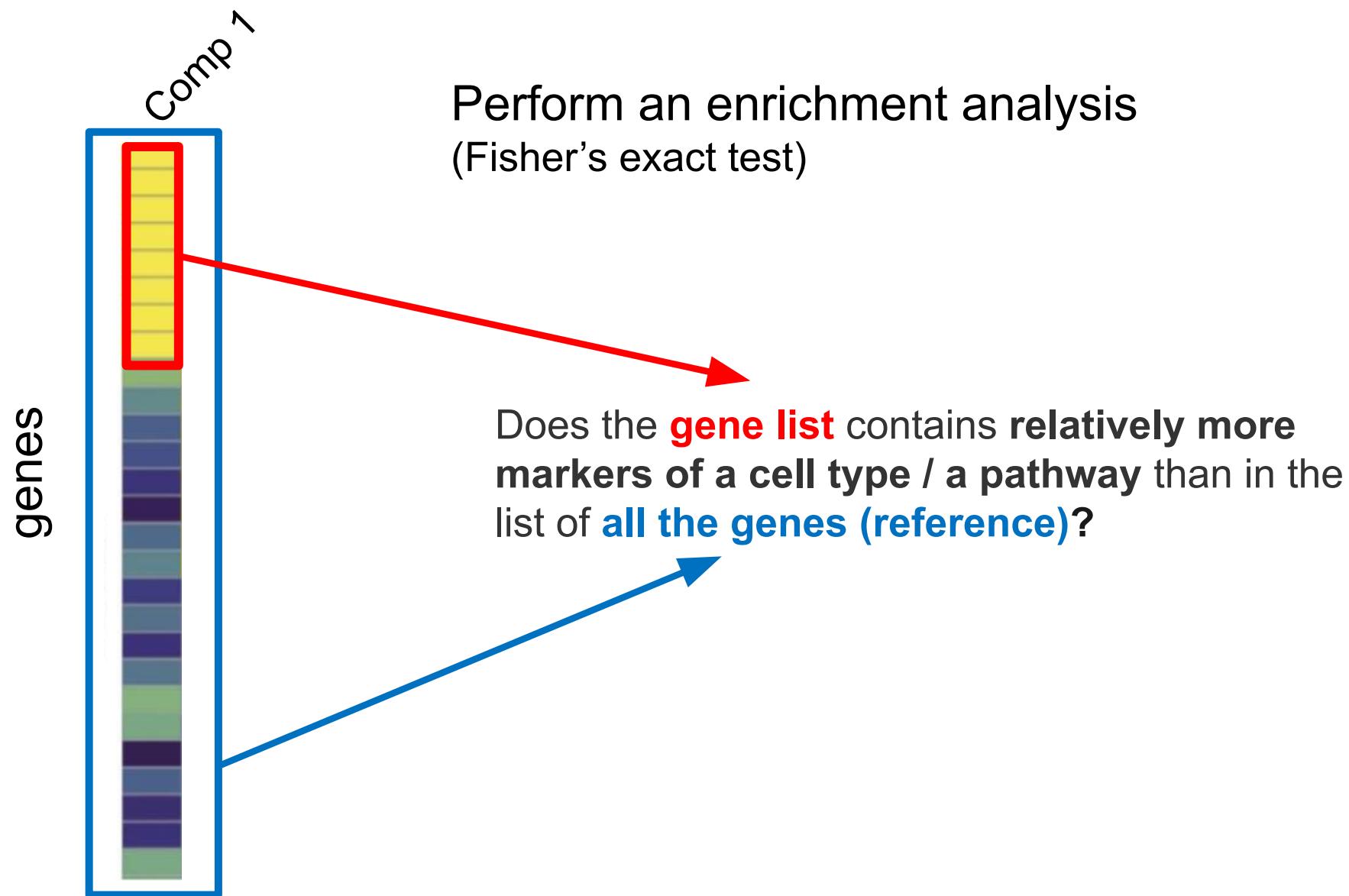


Enrichment Score

P-value of the GSEA test

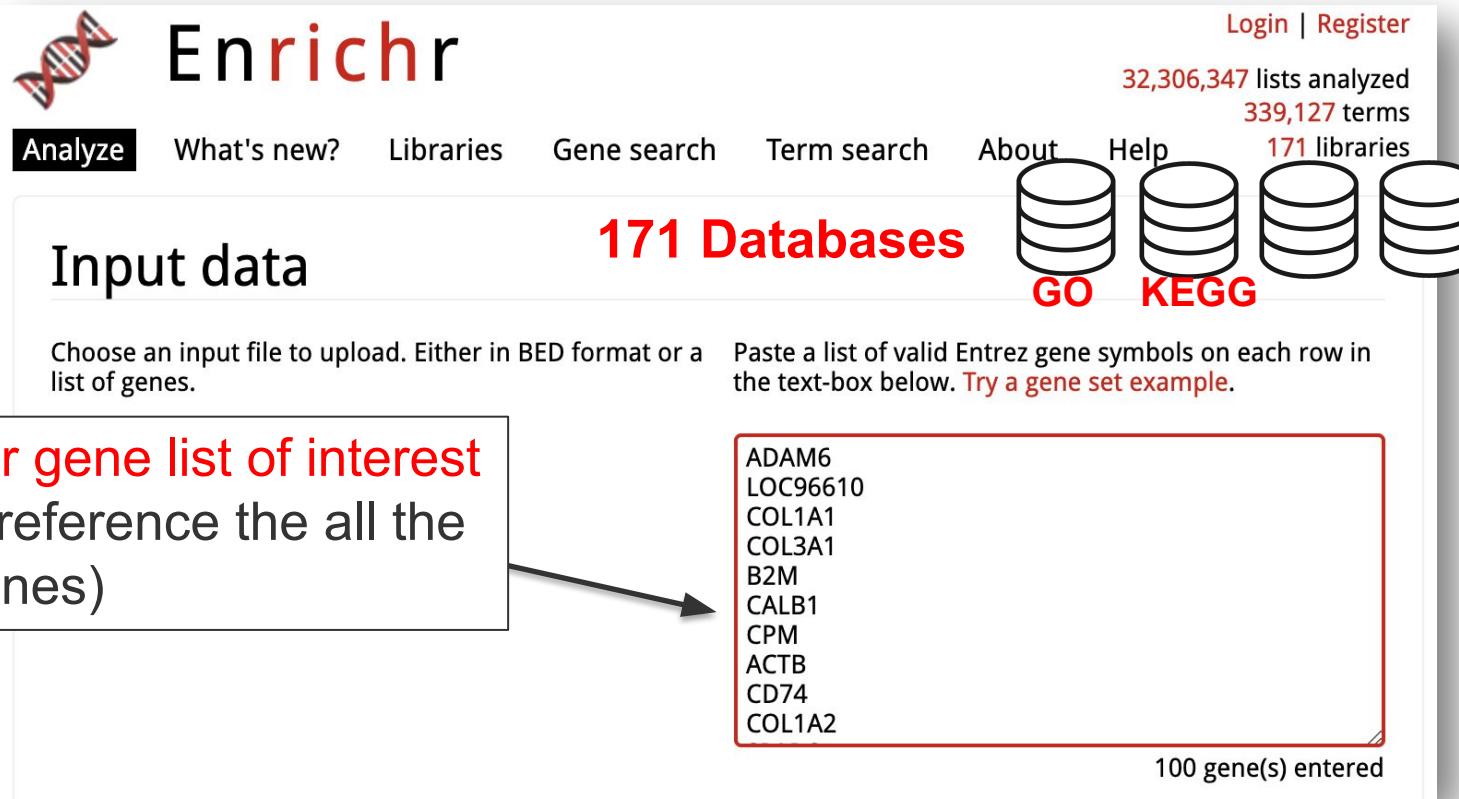
--> Stromal component, Fibroblast?

Cell types from the
CellMatch DataBase

Other option

Output examples

Enrichment analysis with Enrichr



The screenshot shows the Enrichr homepage. At the top right, it displays "32,306,347 lists analyzed" and "339,127 terms". Below this, there are four database icons labeled "GO", "KEGG", and two others partially visible. A red box highlights the text "171 Databases". On the left, a box contains the text "Input data" and "Choose an input file to upload. Either in BED format or a list of genes." An arrow points from this box to a text area where a gene list has been pasted. The pasted genes are:

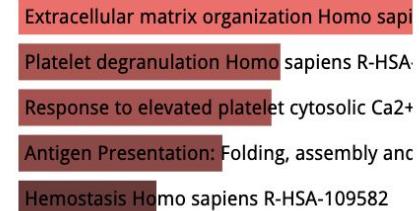
```

ADAM6
LOC96610
COL1A1
COL3A1
B2M
CALB1
CPM
ACTB
CD74
COL1A2
  
```

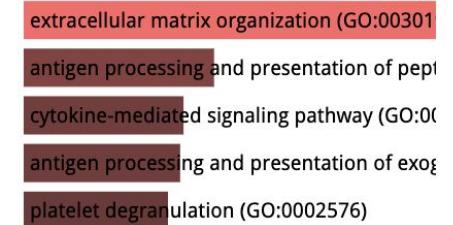
Below the gene list, it says "100 gene(s) entered".

**Paste your gene list of interest
(takes as reference the all the
human genes)**

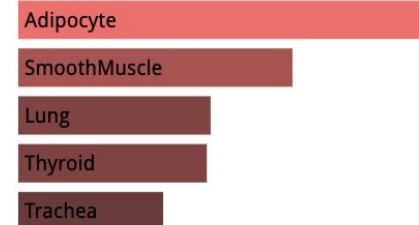
Reactome 2016



GO Biological Process 2018



Human Gene Atlas



Perform enrichment analyses with other external tools

Feature/Tool	DAVID	Enrichr	ToppGene	g:profiler	clusterProfiler	Goplot	BACA	FunMappOne
KEGG pathways	✓	✓	✓	✓	✓		✓	✓
Reactome pathways	✓	✓	✓	✓	✓			✓
Gene Ontology	✓	✓	✓	✓	✓	✓	✓	✓
Graphic representation		✓	✓		✓	✓	✓	✓
Graphic user interface	✓	✓		✓				✓

compExplore Shiny app



INPUT

Gene signature matrix

Input as a csv file
Format: separator = ";" decimal = ","

Browse... results_T_1.csv

Upload complete

The Gene signature matrix corresponds to the output results_T_1.csv in the comet web-app which is already in the requested format (separator = ";" decimal = ",").

Deconvolution method

ICA-based

NMF-based

Cancer type

ALL

Download top markers

Top100 gene markers for each component

Download

OUTPUT

Enrichment analysis

Gene set enrichment analysis results using CellMa

V1

pathway

Non_Small_Cell_Lung_Cancer.Fibroblast
Normal_Fibroblast
Colorectal_Cancer.CancerAssociated_Fibroblast
Head_and_Neck_Cancer.Fibroblast
Oligodendroglioma.Microglial_Cell
Glioma.Astrocyte
B_Cell.Lymphoma.B_Cell
Normal.Circulating_Fetal_Cell
Melanoma.CancerAssociated_Fibroblast
Normal.Stromal_Cell

-log10(pval)

V3

pathway

Normal_1Cell_Stage_Cell_Blastomere
Normal_Secretory_Cell
Ovarian_Cancer.Cancer_Cell
Normal_Alpha_Cell
Astrocytoma.Astrocyte
Melanoma.Macrophage
Colon_Cancer.Stem_Cell
Glioma.Astrocyte
Normal_Mast_Cell
Renal_Cell_Carcinoma.Neutrophil

-log10(pval)

V5

pathway

Colorectal_Cancer.CancerAssociated_Fibroblast
Non_Small_Cell_Lung_Cancer.Fibroblast
Normal_Myofibroblast
Ovarian_Cancer.Mesenchymal_Cell
Normal_Mesangial_Cell
Normal_Bile_Duct_Cell
Head_and_Neck_Cancer.Fibroblast
Normal_Fibroblast
Normal_Idiopathic_Pulmonary_Fibrosis_Cell
Normal_Pneumocyte

-log10(pval)

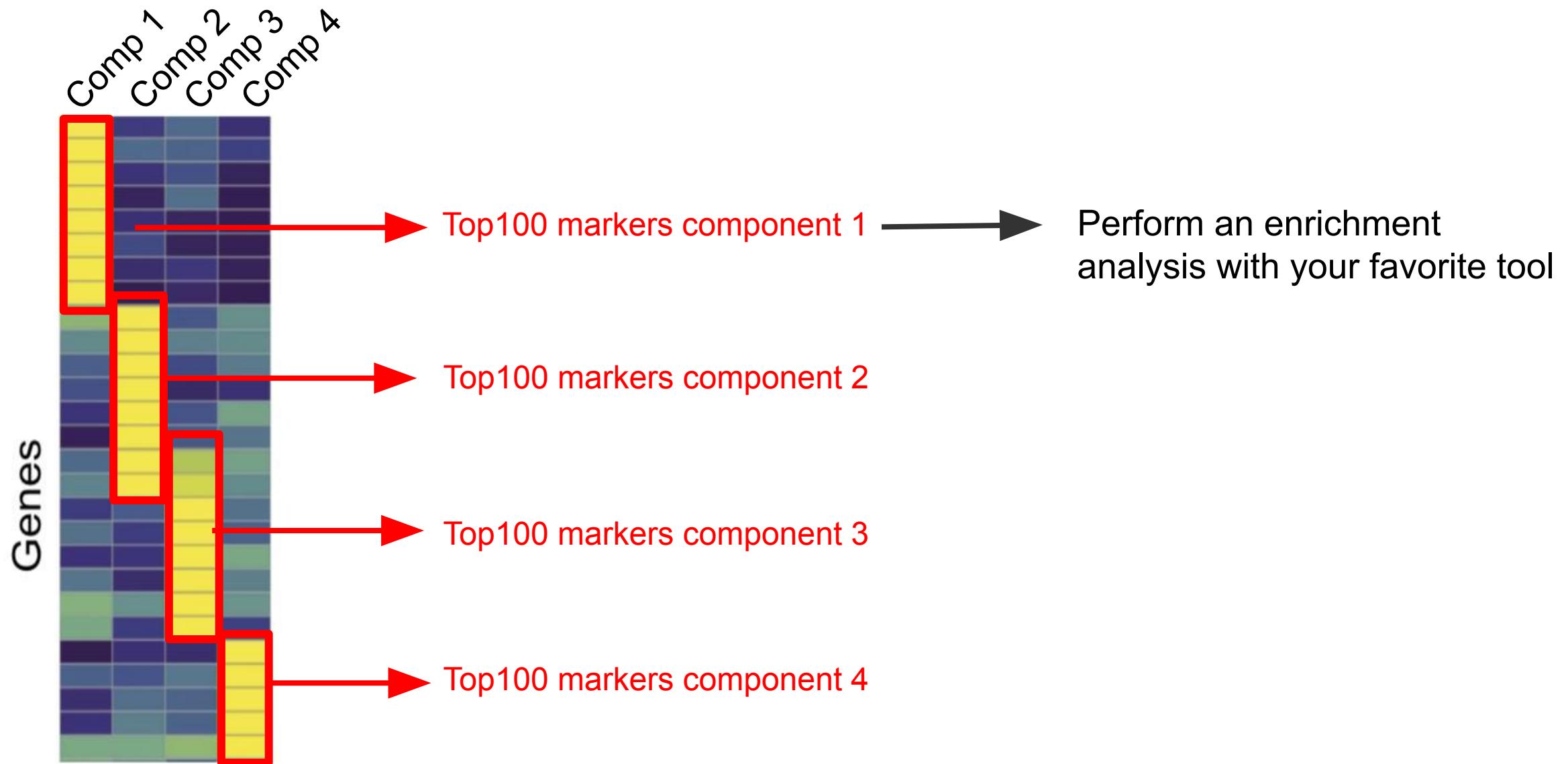
Components enrichment

Proportion vizualisation

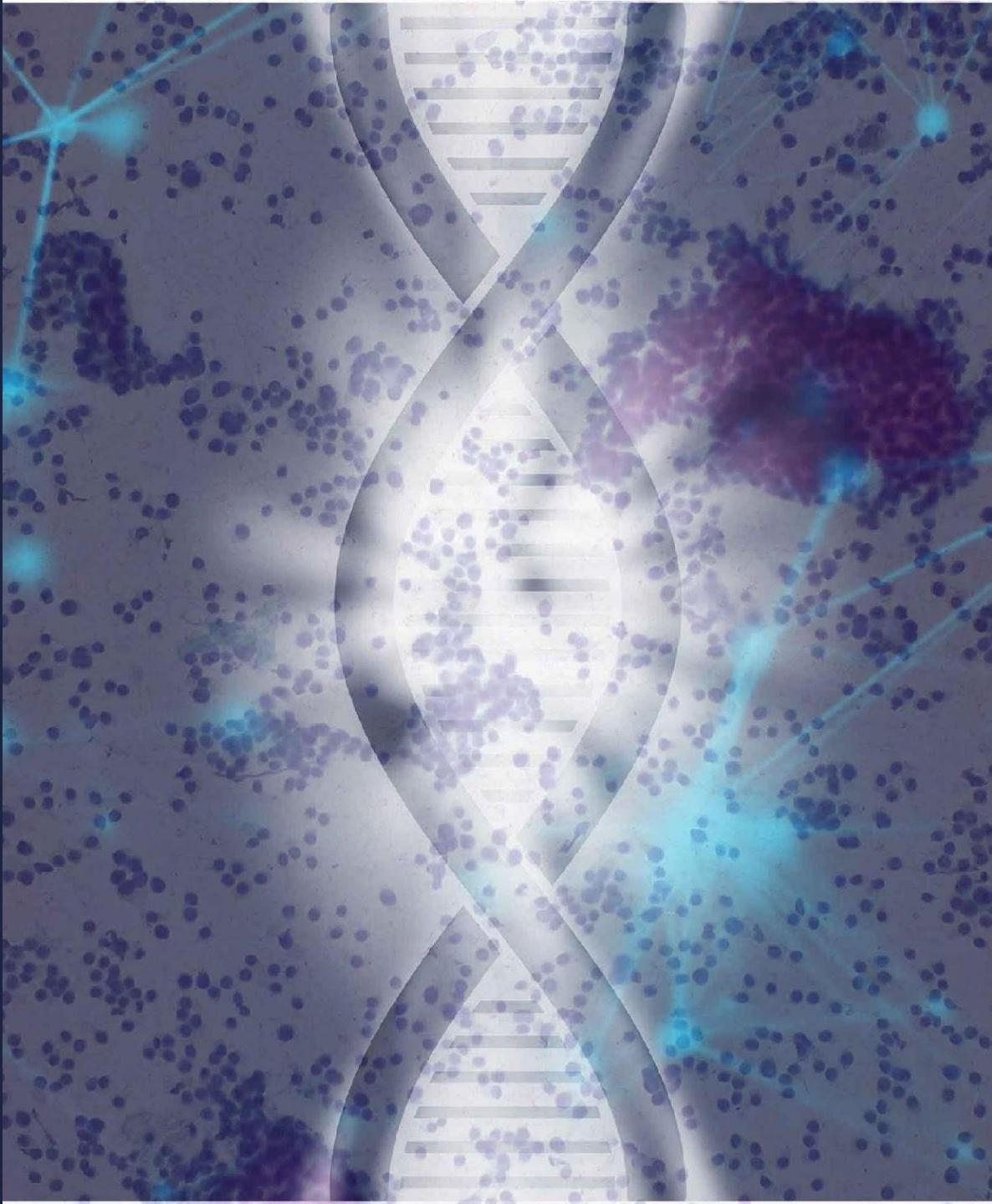
Csv file

	A	B	C	D	E	F
1		V1	V2	V3	V4	V5
2	1 ADAM6	CLU	SFTPB	LOC96610	H19	
3	2 LOC96610	CALB1	FTL	CLU	PLUNC	COL1A1
4	3 COL1A1	PCSK2	CLU	PLUNC	COL1A1	COL3A1
5	4 COL3A1	PGC	SFTPA2	COL1A1	COL3A1	
6	5 B2M	SCGB3A2	TPT1	FGA	COL1A2	
7	6 CALB1	MYCL1	NAPSA	CALCA	PLUNC	
8	7 CPM	SCN3A	CEACAM6	FGG	IGF2	
9	8 ACTB	BAI1	CTSD	COL3A1	SPARC	
10	9 CD74	C16orf89	PLUNC	FGB	SFTPB	
11	10 COL1A2	GKN2	EEF1A1	FN1	ADAM6	
12	11 SPARC	GP2	CALCA	CEACAM6	CHGB	
13	12 TMSL3	AMBP	MSLN	GAPDH	CEACAM5	
14	13 HSP90B1	TMEM59L	FTH1	COL1A2	CALCA	
15	14 HLA-B	HPCAL4	AKR1C1	MUC5B	CEACAM6	
16	15 IGJ	GRIK1	MUC5B	SFTPC	COL6A3	
17	16 PABPC1	OBP2A	P4HB	SFTPA2	SLC34A2	
18	17 ACTG1	C1orf95	ACTG1	FTL	TMSL3	
19	18 PSAP	CHRDL2	PCSK2	CTSD	SFTPA2	
20	19 GAPDH	ADHFE1	SFTPC	CALB1	FLNA	
21	20 HLA-A	PCDHGA4	MUC1	SLC34A2	TIMP3	
22	21 HLA-DRA	GLYATL3	PABPC1	CPM	CPM	
23	22 CEACAM6	KRT40	LGALS3BP	SPARC	HMGB3	
24	23 LUM	ADRB1	EEF2	PCSK2	ODC1	
25	24 CCT2	LCN15	SFTPA1	MSLN	ATP1A1	
26	25 UBC	PLA2G10	FGB	CEACAM5	S100A6	
27	26 HLA-C	CBLN2	ACTB	HP	NDRG1	
28	27 KRT7	SCN2A	SCGB3A2	SFTPA1	GNAS	
29	28 BGN	LIMS3-LOC44	FGA	ENO1	VIM	
30	29 CALR	ITLN2	RPL8	PCSK1	SFTPC	
31	30 DHHR	STAG2	CDF2	HSDBOR1	RGN	

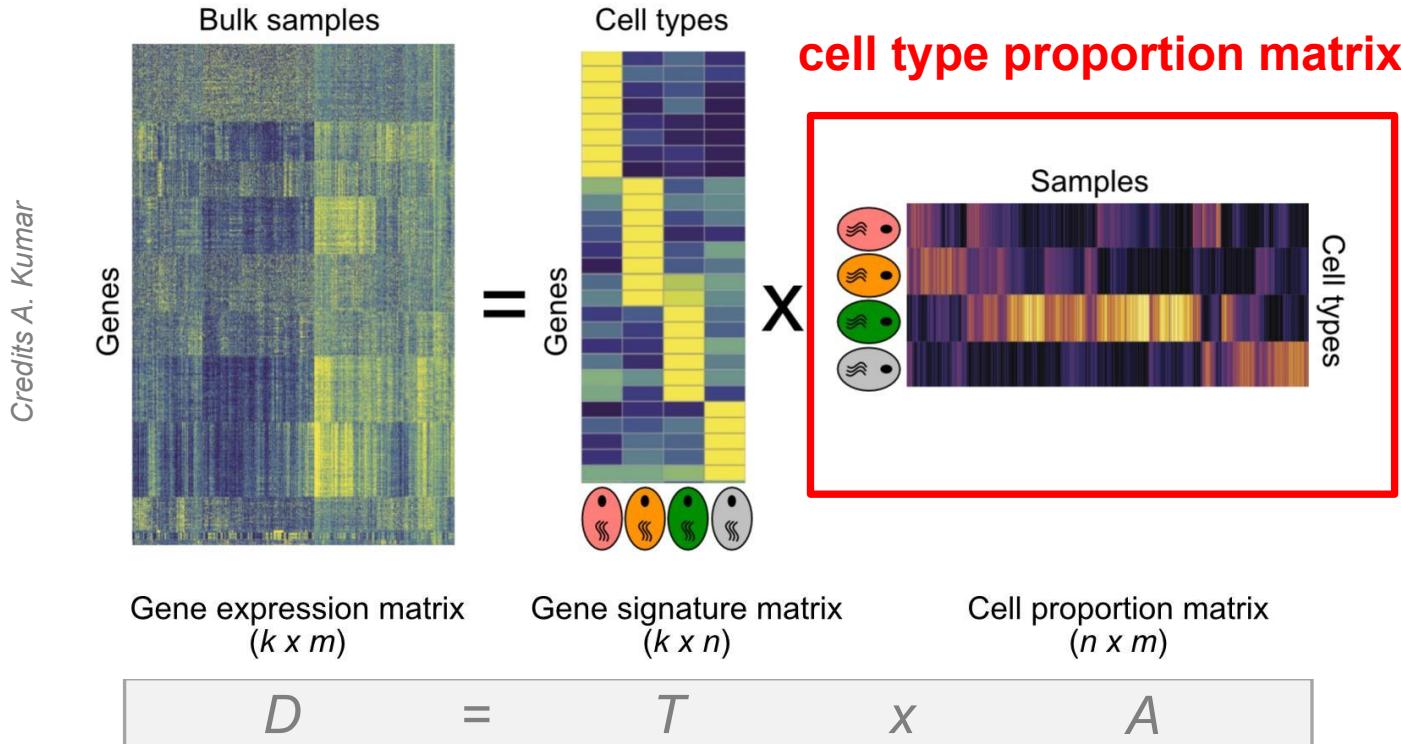
Interpret the components identified



Visualize the cell type proportion matrix



Visualize the cell type proportion matrix



- Is a given sample highly heterogeneous in its composition?
- Are all the different samples similar in their cell type composition ?

compExplore Shiny app



compExplore [About](#) [CSV-convertor](#) [Number of CellTypes](#) [Components enrichment](#) [Proportion vizualisation](#)

PUT

Cell proportion matrix

Input as a csv file
Format: separator = ";" decimal = ","

[Browse...](#) No file selected

The Gene proportion matrix corresponds to the output results_A_1.csv in the cometh web-app which is already in the requested format (separator = ";" decimal = ",").

Select samples

No choices here yet !!

Select cell types

No choices here yet !!

Guide

Vizualisation plots

OUPUT

Heatmap of the proportion matrix

Heatmap of the proportion matrix

IC2, IC1, IC5, IC4, IC3

0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1

Focus on a selected sample

Cell types abundance for this sample

0.7
0.6
0.5
0.4
0.3
0.2
0.1

IC1, IC2, IC3, IC4, IC5

Focus on a selected cell type:

distribution among samples

0.8
0.6
0.4

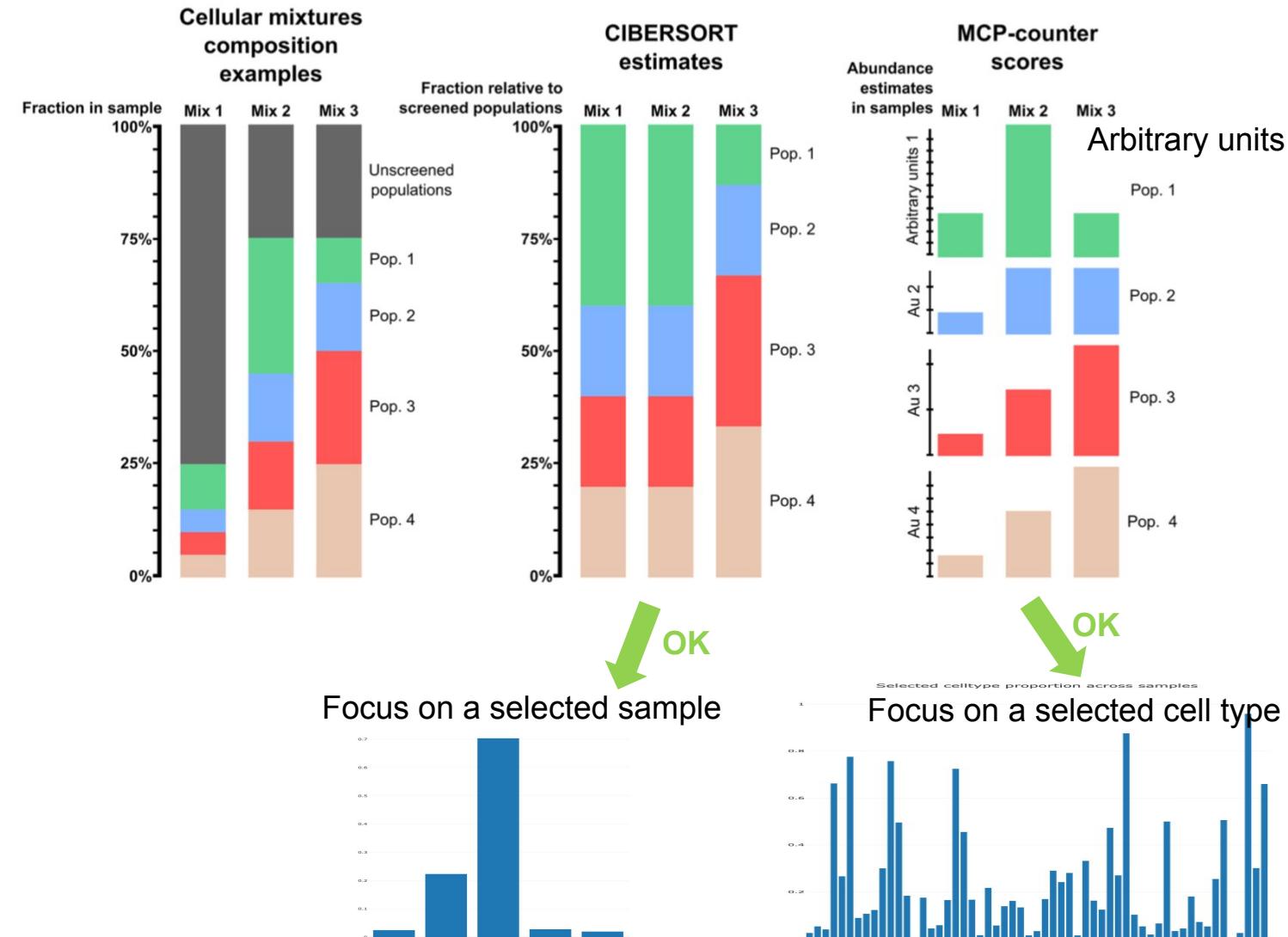
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Visualize the cell type proportion matrix

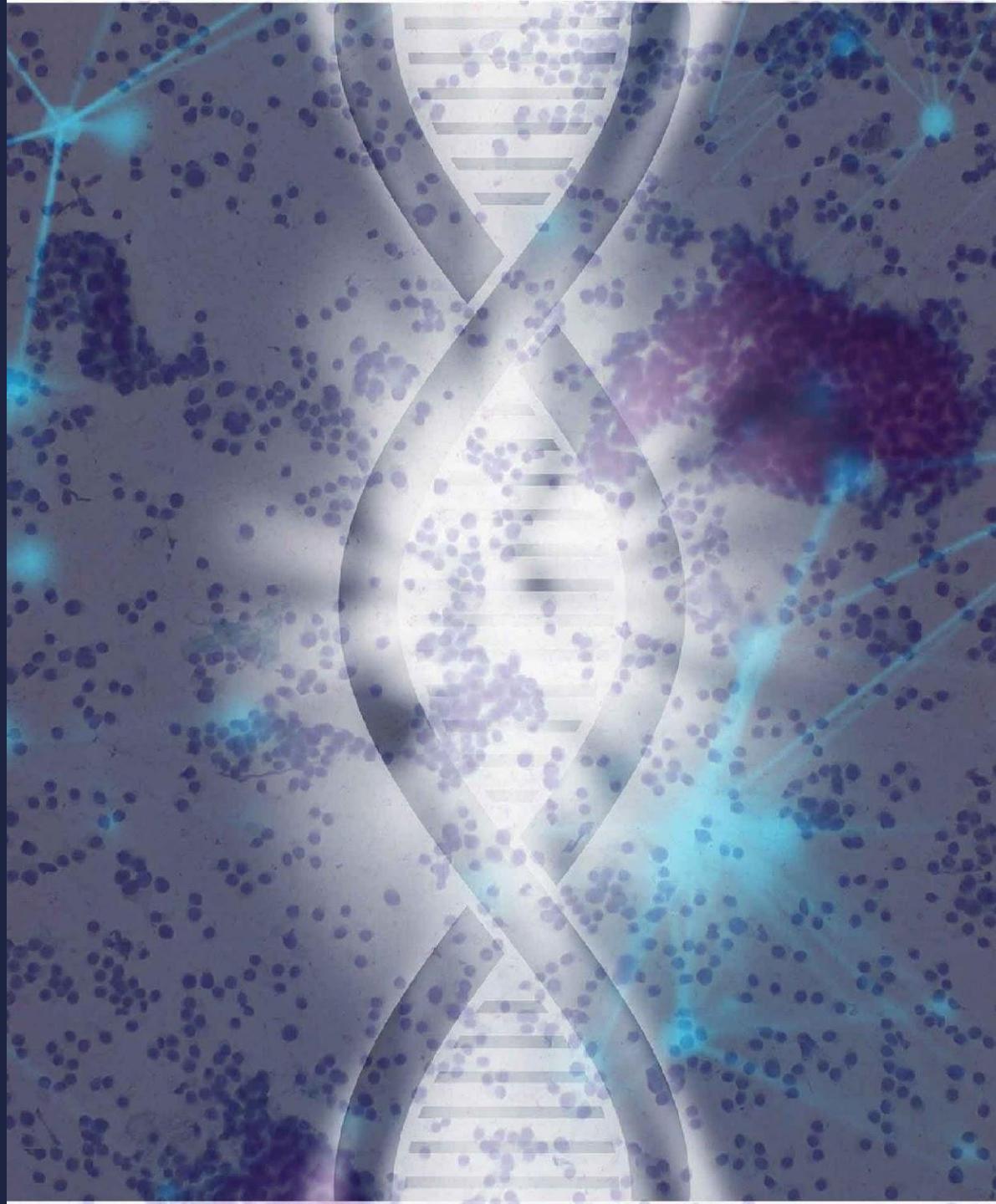


- (1) CIBERSORT-ABS, EPIC and quanTlseq can be used for both **inter- and intra- sample comparisons** i.e. comparing one cell-type within one sample and across samples is possible
- (2) CIBERSORT can be used only for **intra-sample comparisons** i.e. comparing different cell-types within each sample
- (3) MCP-Counter, TIMER and xCell (not provided yet in the comet web app) can be used only for **inter- sample comparisons** i.e. to compare one cell-type across multiple samples

Petitprez et al., 2018 Cancer Immunol Immunother



Go further in biological interpretation



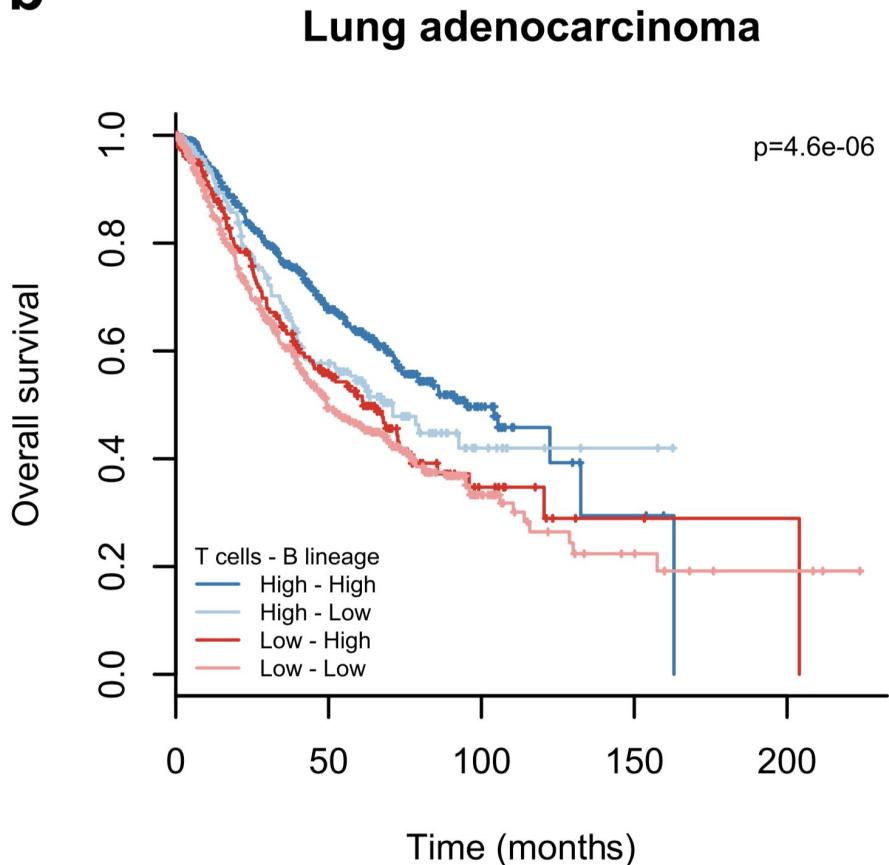
Relate cell type proportions to clinical annotations

Example of the prognosis

Tools

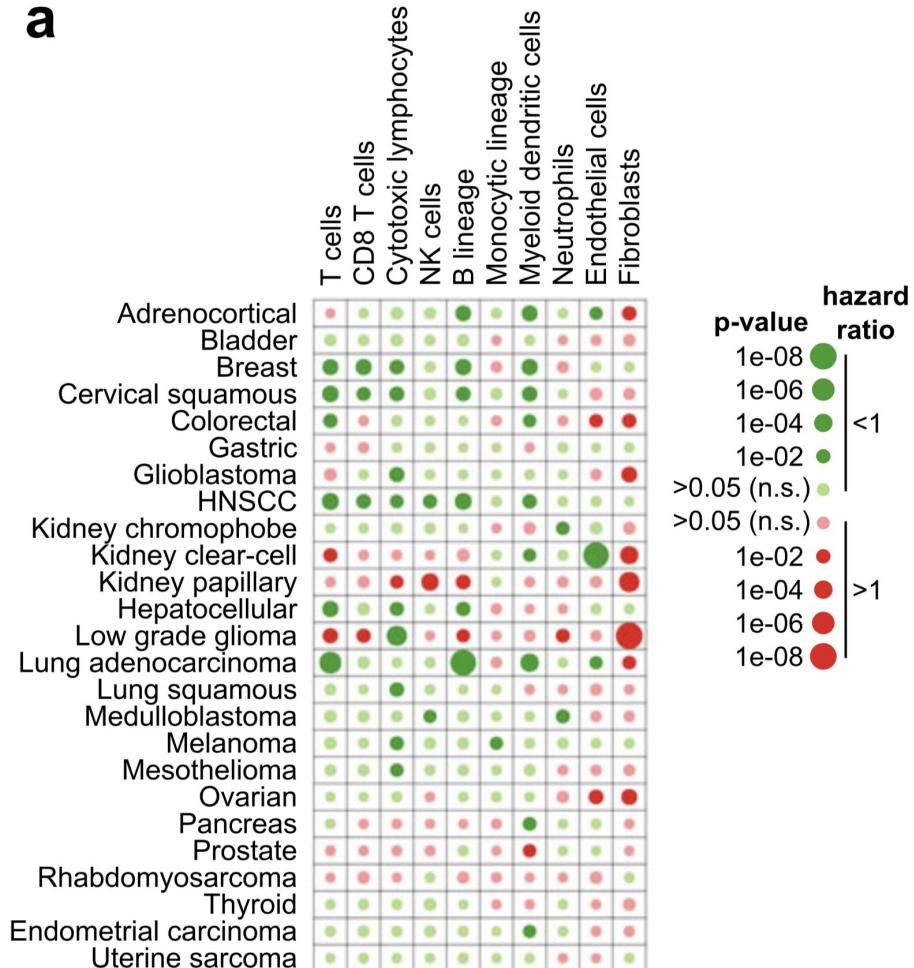


b



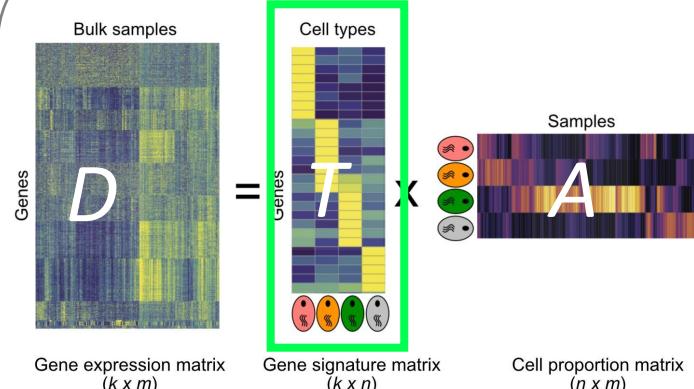
Becht et al 2016, Genome Biology

a



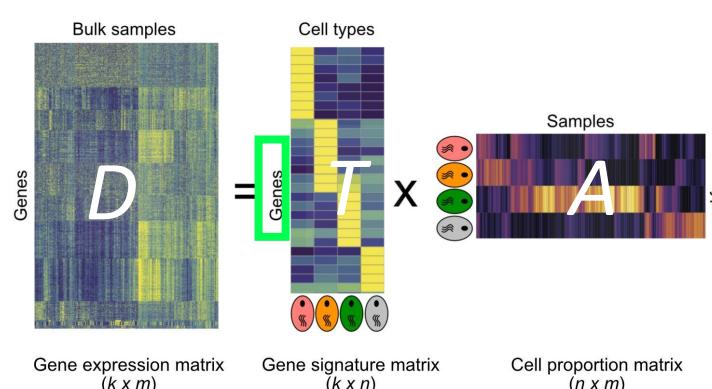
Pay attention to...

Supervised



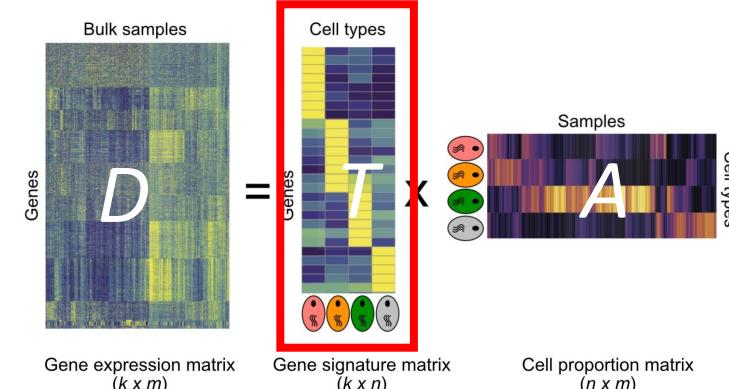
T matrix known

Semi-supervised



Gene markers known

Unsupervised



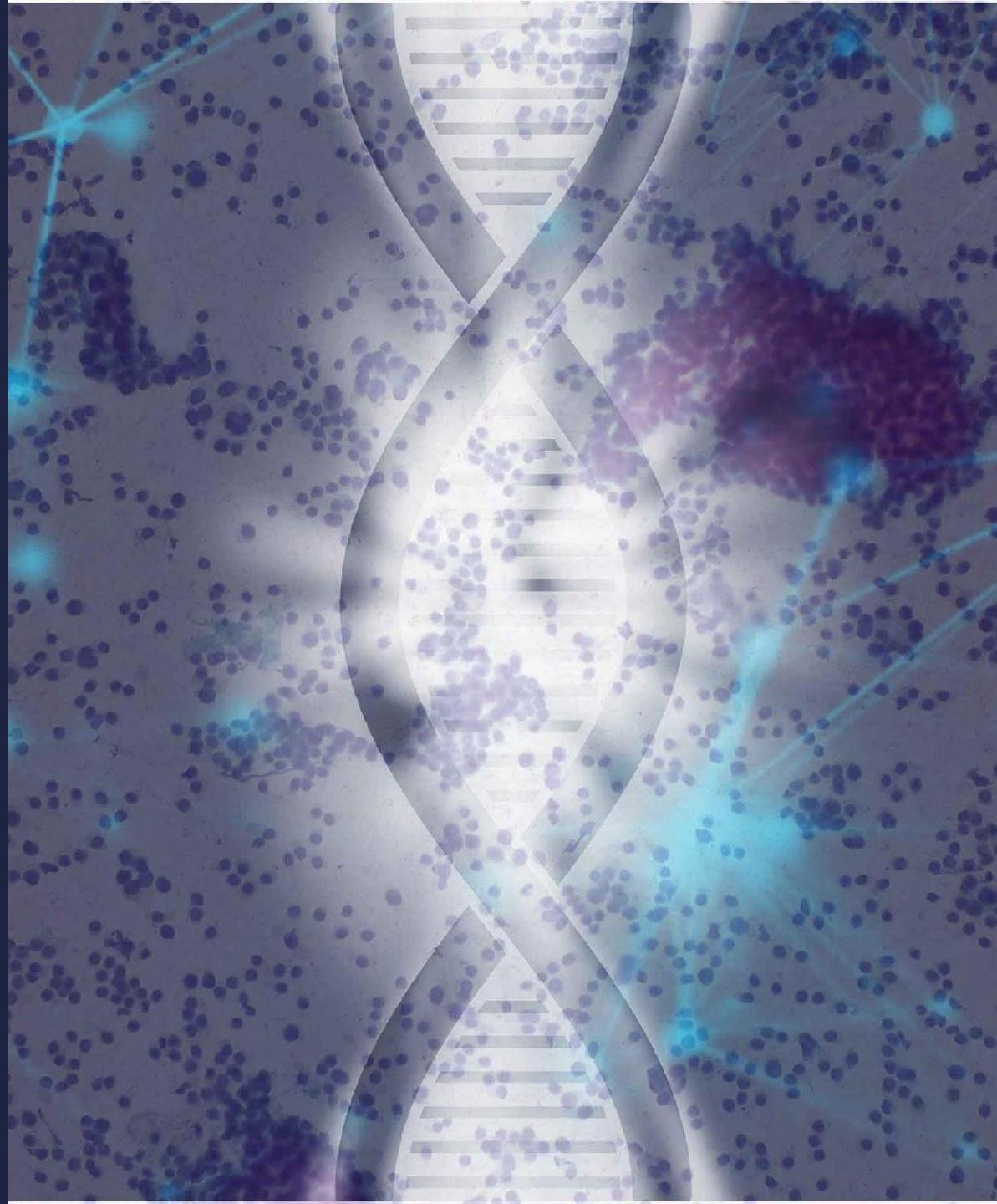
T matrix unknown

- Are the cell type profiles reliable?
- Are the cell type profiles appropriate regarding the cancer types/ tissue you are looking at?

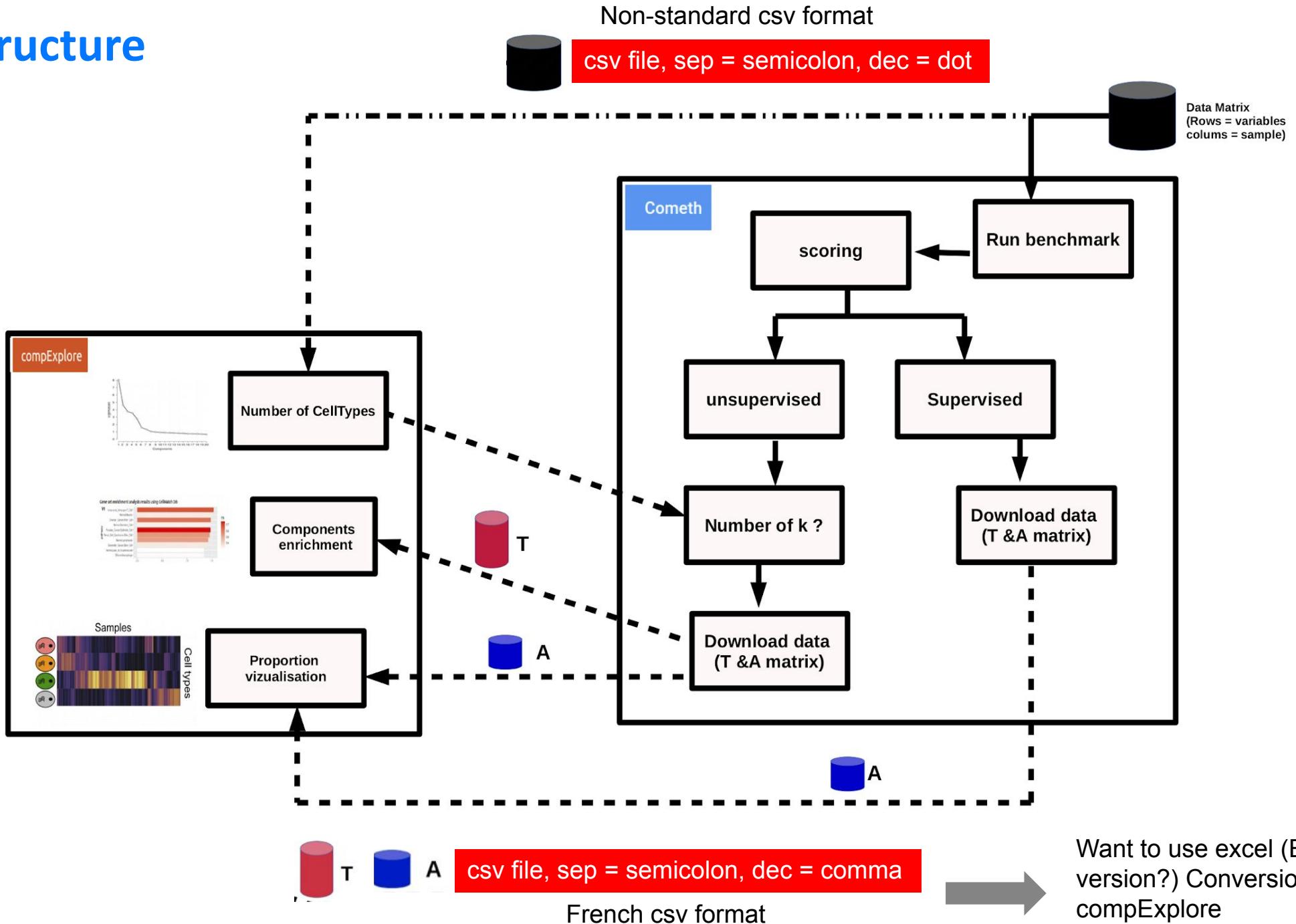
- Are the gene markers reliable/robust ?
- Are gene markers appropriate regarding the cancer type/ tissue you are looking at?

- When choosing k , did I choose a good granularity ?
 - Seem components be a mix between several cell types?
 - Are there several components corresponding the same signal?

Overall structure input/output format



Overall structure



compExplore Shiny app



compExplore About CSV-convertisor Number of CellTypes Components enrichment Proportion vizualisation

Your csv file

Browse... No file selected

Note that output from the cometh web-app are in the french-format (Separator = ";" Decimal = ",")

Separator
 Semicolon
 Comma
 Tab
 Space

Convert you csv file into:

Filename (without csv extension)

Decimal
 Comma
 Dot

Format
 English
 French
 NonStandard

English - Separator = "," Decimal = "."

French - Separator = ";" Decimal = ","

NonStandard - Separator = ";" Decimal = ","

Download your converted csv file

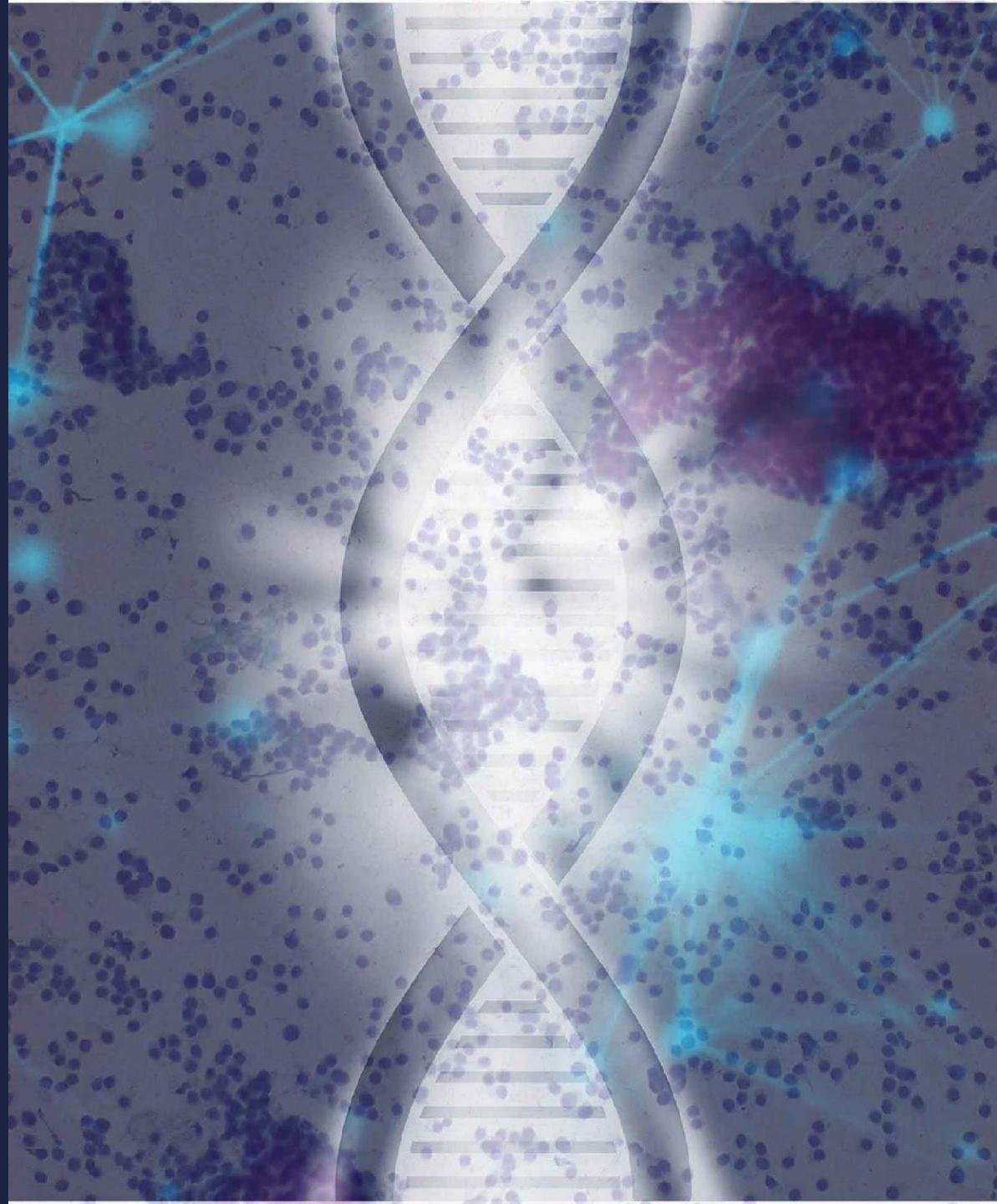
Convert

This module can be useful if you are, for instance, using an english version of excel: output of the cometh app are csv files in the french format. Convert them into the english format will allow you to open them directly in excel.

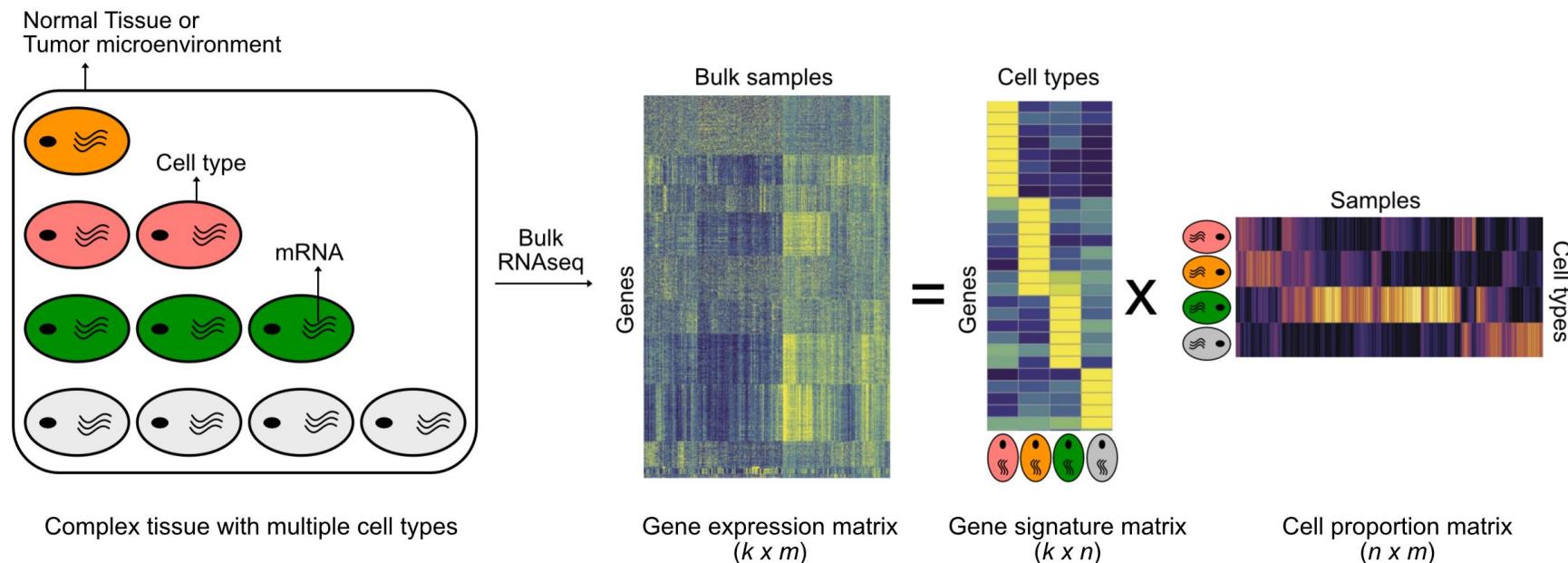
Open Cometh' outputs in english version of Excel

Prepare input data for Cometh web-app

Examples of success stories



Resolving cell types from complex tissue genomic data : RECAP



- **DeconRNAseq** (~160 | Apr, 2013 | <https://doi.org/10.1093/bioinformatics/btt090>)
- **CellMix** (~180 | Sep, 2013 | <https://doi.org/10.1093/bioinformatics/btt351>)
- **CIBERSORT** (~2000 | Mar, 2015 | <https://doi.org/10.1038/nmeth.3337>)
- **MCP-Counter** (~350 | Oct, 2016 | <https://doi.org/10.1186/s13059-016-1070-5>)
- **TIMER2.0** (~500 | Jul, 2017 | <https://doi.org/10.1093/nar/gkaa407>)
- **Xcell** (~400 | Nov, 2017 | <https://doi.org/10.1186/s13059-017-1349-1>)
- **EPIC** (~100 | Nov, 2017 | <https://doi.org/10.7554/eLife.26476>)
- **QuantiSeq** (~50 | May, 2019 | <https://doi.org/10.1186/s13073-019-0638-6>)

Table 1. Overview of cell type quantification methods providing gene signatures for immuno-oncology

Tool	Abbrev.	Type	Score	Comparisons	Algorithm	Cell types	Reference
CIBERSORT	CBS	D	Immune cell fractions, relative to total immune cell content	Intra	ν -support vector regression	22 immune cell types	Newman et al. (2015)
CIBERSORT abs. mode	CBA	D	Score of arbitrary units that reflects the absolute proportion of each cell type	Intra, inter	ν -support vector regression	22 immune cell types	Newman et al. (2015, 2018)
EPIC	EPC	D	Cell fractions, relative to all cells in sample	Intra, inter	constrained least square regression	6 immune cell types, fibroblasts, endothelial cells	Racle et al. (2017)
MCP-counter	MCP	M	Arbitrary units, comparable between samples	Inter	mean of marker gene expression	8 immune cell types, fibroblasts, endothelial cells	Becht et al. (2016)
quanTIseq	QTS	D	Cell fractions, relative to all cells in sample	Intra, inter	constrained least square regression	10 immune cell types	Finotello et al. (2017)
TIMER	TMR	D	Arbitrary units, comparable between samples (not different cancer types)	Inter	linear least square regression	6 immune cell types	Li et al. (2016)
xCell	XCL	M	Arbitrary units, comparable between samples	Inter	ssGSEA (Hänzelmann et al., 2013)	64 immune and non-immune cell types	Aran et al. (2017)

Note: Methods can be conceptually distinguished in marker-gene-based approaches (M) and deconvolution-based approaches (D). The output scores of the methods have different properties and allow either intra-sample comparisons between cell types, inter-sample comparisons of the same cell type, or both. All methods come with a set of cell type signatures ranging from six immune cell types to 64 immune and non-immune cell types.

Table 2. Guidelines for method selection

Cell type	Recommended methods	Overall performance	Absolute score	No background predictions
B cell	EPIC MCP-counter	++	++	+
T cell CD4+		++	-	-
T cell CD4+ non-regulatory	EPIC	++	++	-
	xCell	++	-	++
T cell regulatory	quanTIseq	+	++	+
	xCell	+	-	++
T cell CD8+	quanTIseq	++	++	-
	EPIC	++	++	-
Natural Killer Cell	MCP-counter	++	-	-
	xCell	+	-	++
Macrophage / Monocyte	EPIC	++	++	+
	MCP-counter	++	-	-
Cancer-associated fibroblast	xCell	-	++	
	EPIC	+	++	+
Endothelial Cell	MCP-counter	++	-	-
	EPIC	++	++	+
Dendritic cell	MCP-counter	++	-	-
	xCell	++	-	++
Dendritic cell	→	None of the methods can be recommended to estimate overall DC content. MCP-counter and quanTIseq can be used to profile mDCs.		

Neoantigen-directed immune escape in lung cancer evolution

Rachel Rosenthal, Elizabeth Larose Cadieux, Roberto Salgado, Maise Al Bakir, David A. Moore, Crispin T. Hiley, Tom Lund, Miljana Tanić, James L. Reading, Kroopa Joshi, Jake Y. Henry, Ehsan Ghorani, Gareth A. Wilson, Nicolai J. Birkbak, Mariam Jamal-Hanjani, Selvaraju Veeriah, Zoltan Szallasi, Sherene Loi, Matthew D. Hellmann, Andrew Feber, Benny Chain, Javier Herrero, Sergio A. Quezada, Jonas Demeulemeester, Peter Van Loo, Stephan Beck, Nicholas McGranahan , Charles Swanton  & The TRACERx consortium -Show fewer authors

Nature 567, 479–485(2019) | Cite this article

47k Accesses | 163 Citations | 359 Altmetric | Metrics

Cancer Research UK Lung Cancer Centre of Excellence, University College London

Cancer Institute, University College London, London, UK

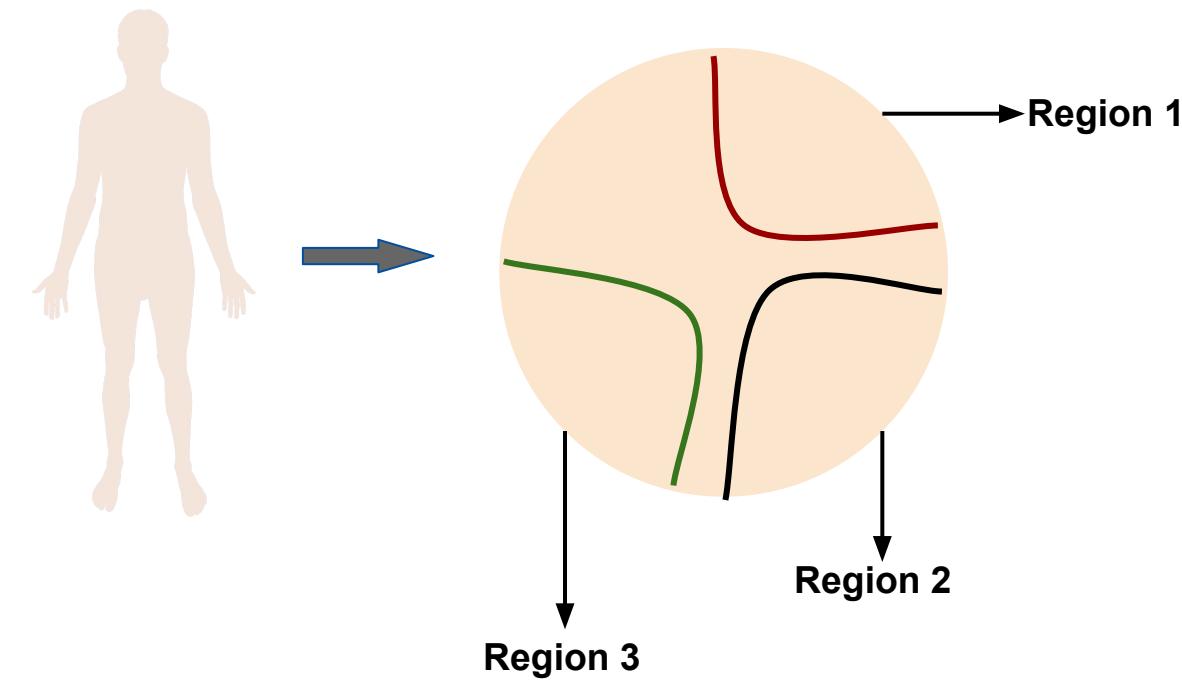
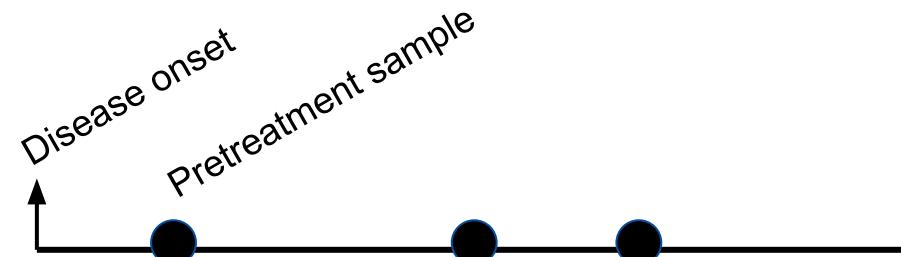
Cancer Genome Evolution Research Group, University College London Cancer

Institute, University College London, London, UK

<https://doi.org/10.1038/s41586-019-1032-7>

nature

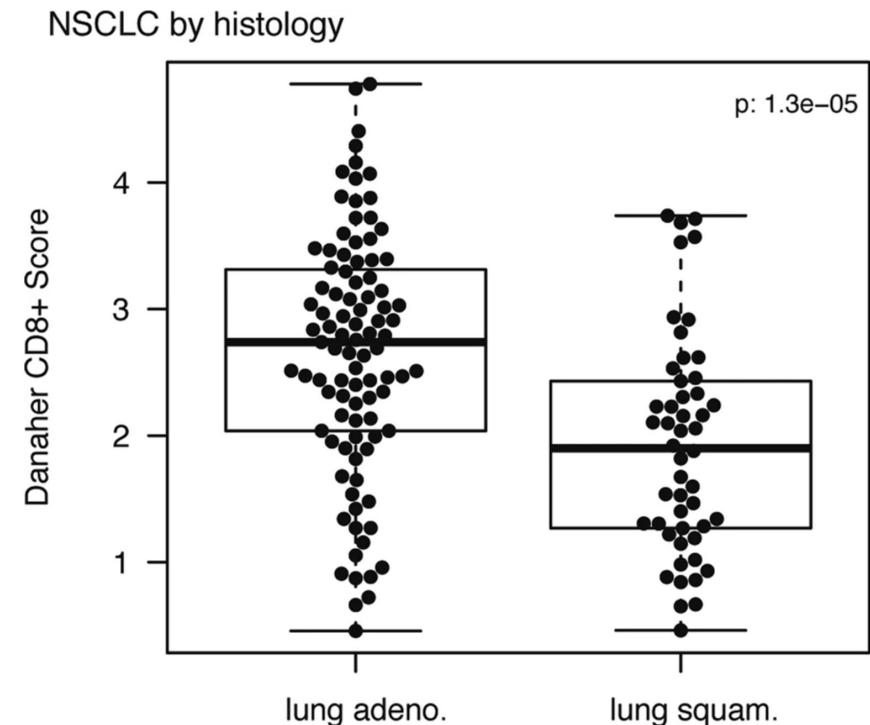
TRACERx 100 cohort

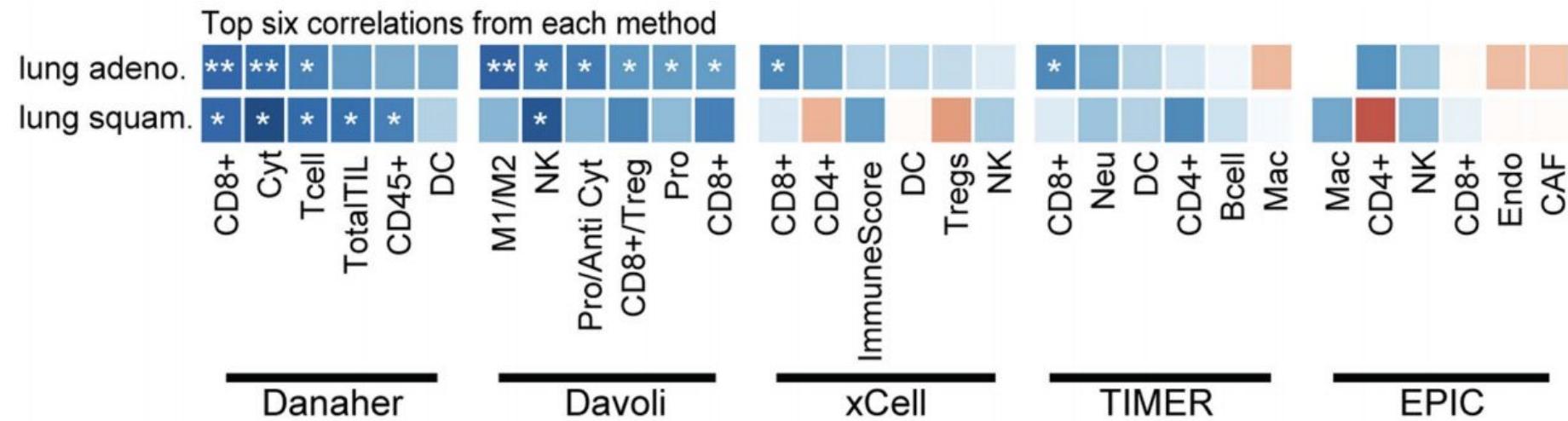


164 RNA-seq samples from 64 non-small-cell lung cancer (NSCLC)

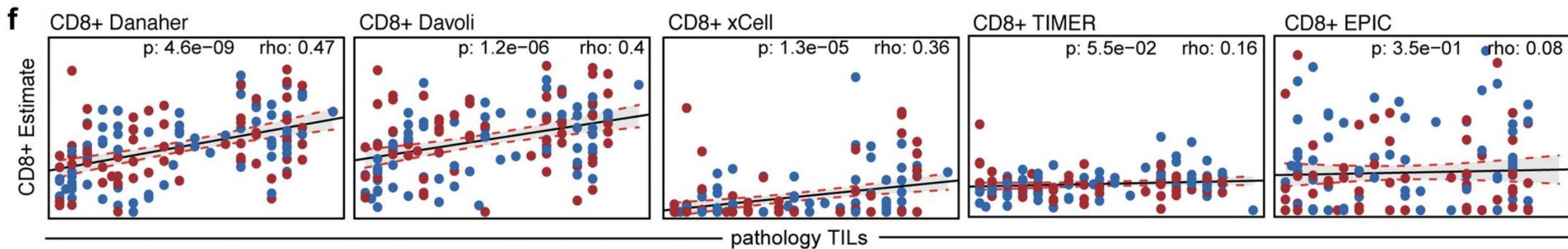
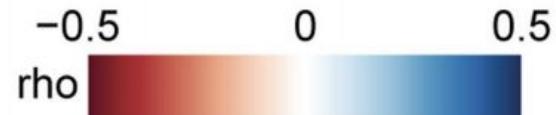
Tumour-infiltrating lymphocyte (TIL) histopathology estimates ($n=234$) from 83 NSCLC

~258 tumor regions from 88 patients (TRACERx 100 cohort)





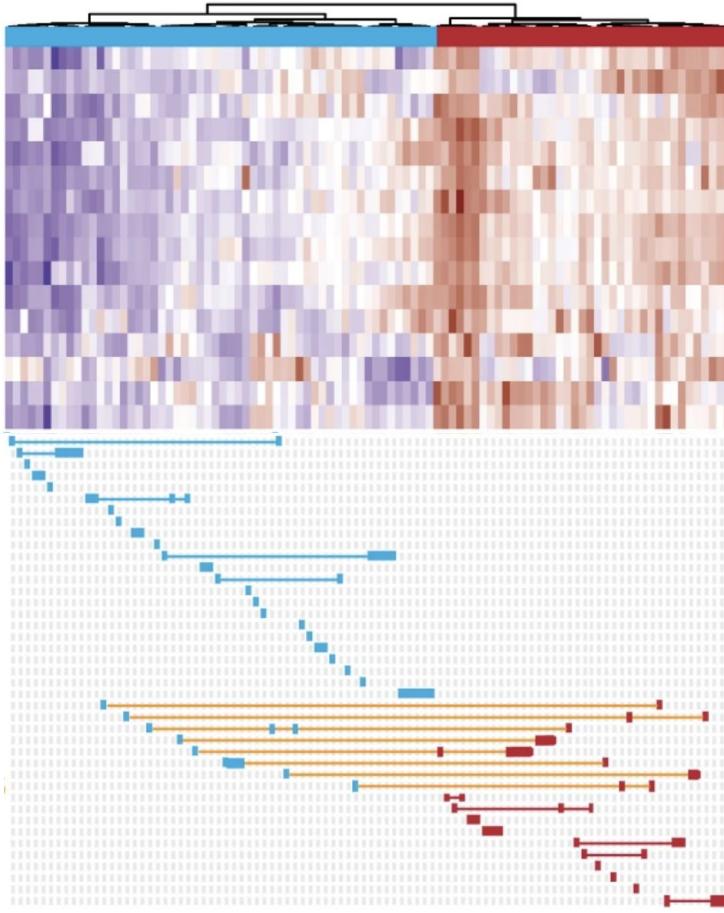
** FDR corrected p-value < 0.01
* FDR corrected p-value < 0.05



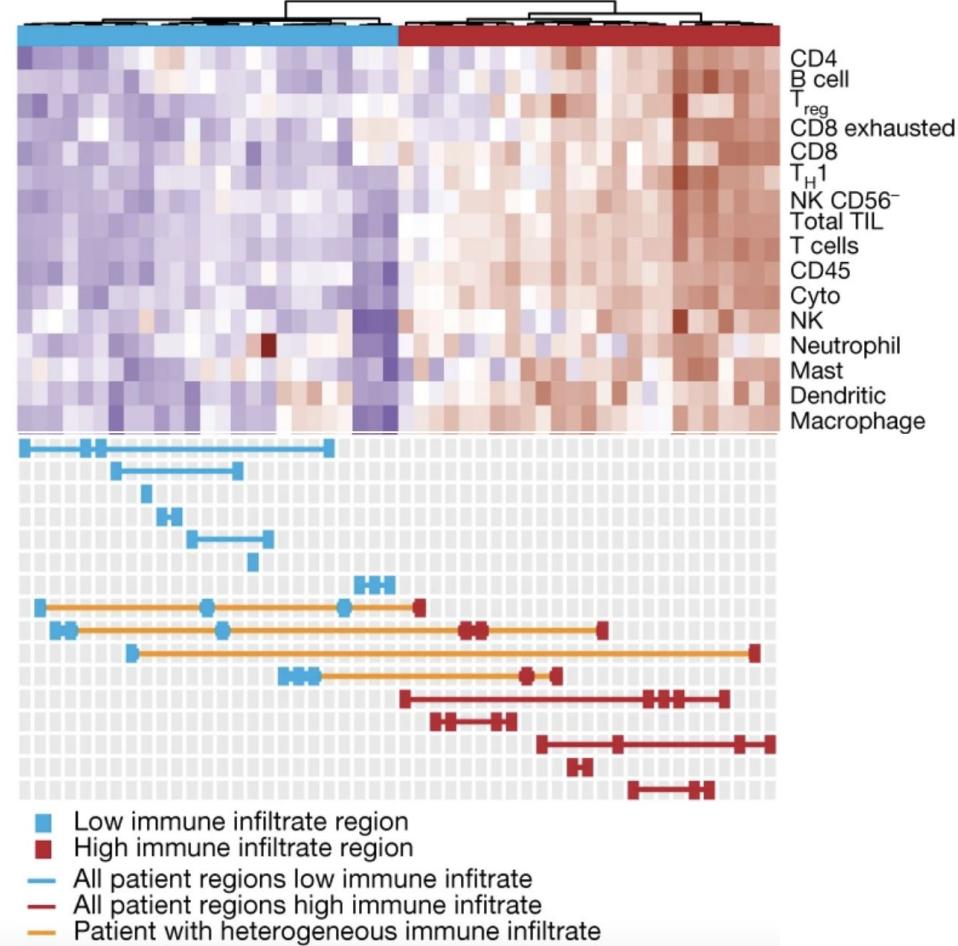
- Lung adenocarcinoma
- Lung squamous cell carcinoma

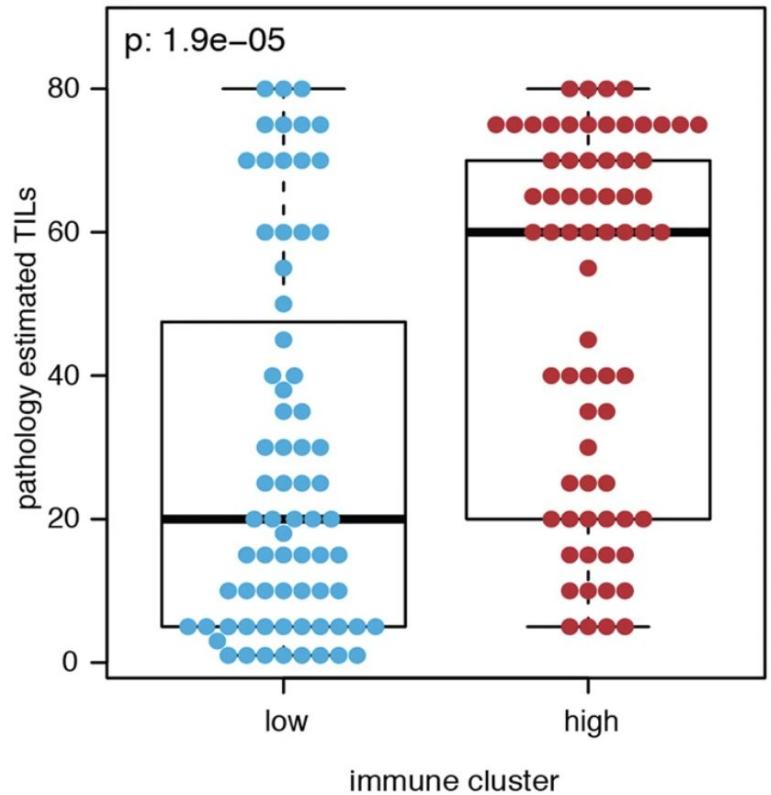
n=140 tumor regions

a Lung adenocarcinoma



b Lung squamous cell carcinoma





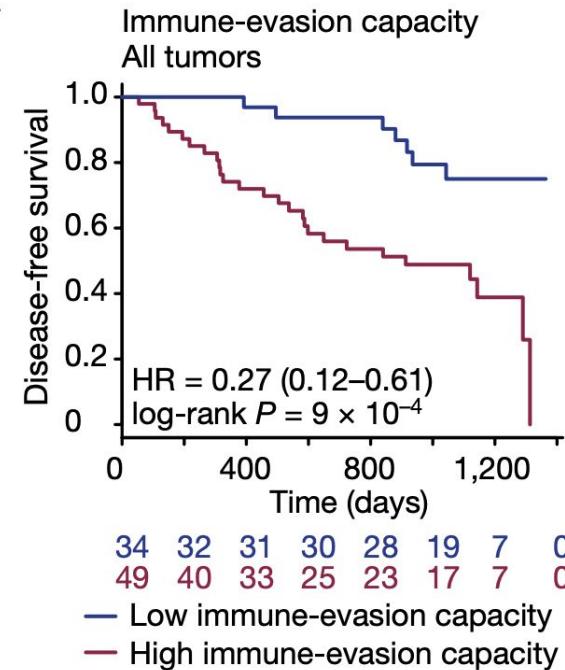
C Immune-evasion capacity

Low immune evasion

- High immune infiltration or no immune escape
- { No immune editing
No HLA LOH
No antigen-processing defect}

High immune evasion

- Low/mixed immune infiltration and immune escape
- { Immune editing /
HLA LOH /
Antigen-processing defect}



Computational methods of supervised immune cell type enumeration can identify clinically relevant biology

Super enhancers define regulatory subtypes and cell identity in neuroblastoma

Moritz Gartlgruber, Ashwini Kumar Sharma, Andrés Quintero, Daniel Dreidax, Selina Jansky, Young-Gyu Park, Sina Kreth, Johanna Meder, Daria Doncevic, Paul Saary, Umut H. Toprak, Naveed Ishaque, Elena Afanasyeva, Elisa Wecht, Jan Koster, Rogier Versteeg, Thomas G. P. Grünewald, David T. W. Jones, Stefan M. Pfister, Kai-Oliver Henrich, Johan van Nes, Carl Herrmann  & Frank Westermann 

Nature Cancer **2**, 114–128(2021) | Cite this article

1651 Accesses | **1** Citations | **38** Altmetric | Metrics

Health Data Science Unit, Medical Faculty Heidelberg and BioQuant, Heidelberg,

Germany

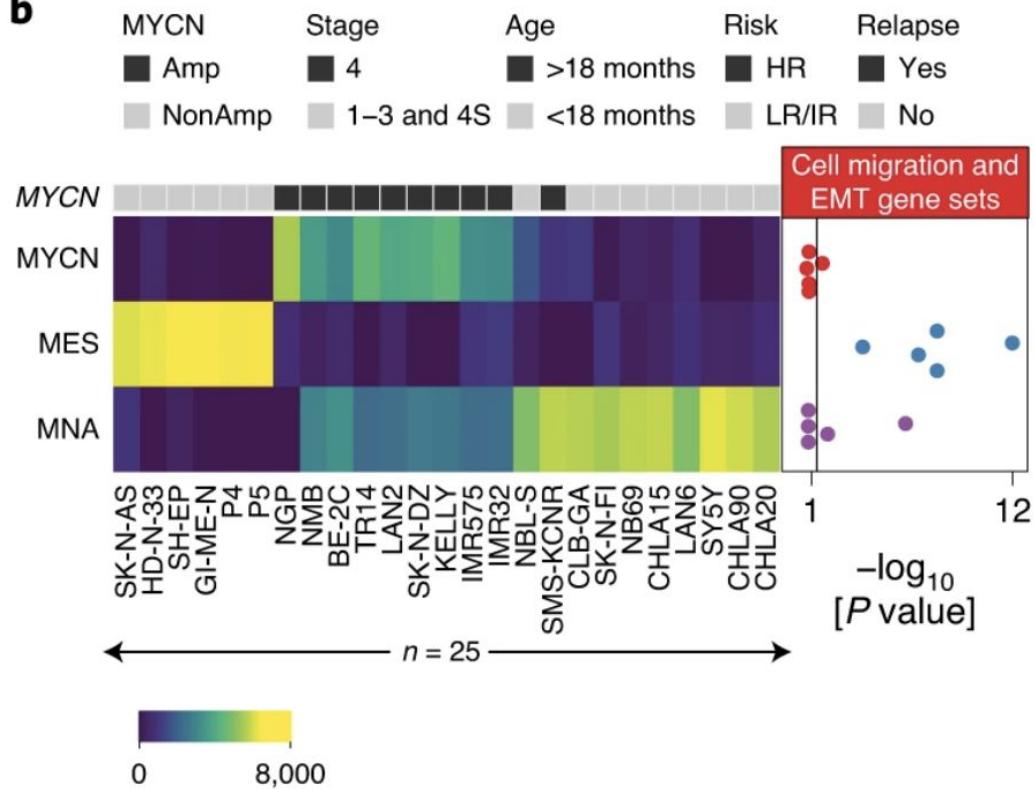
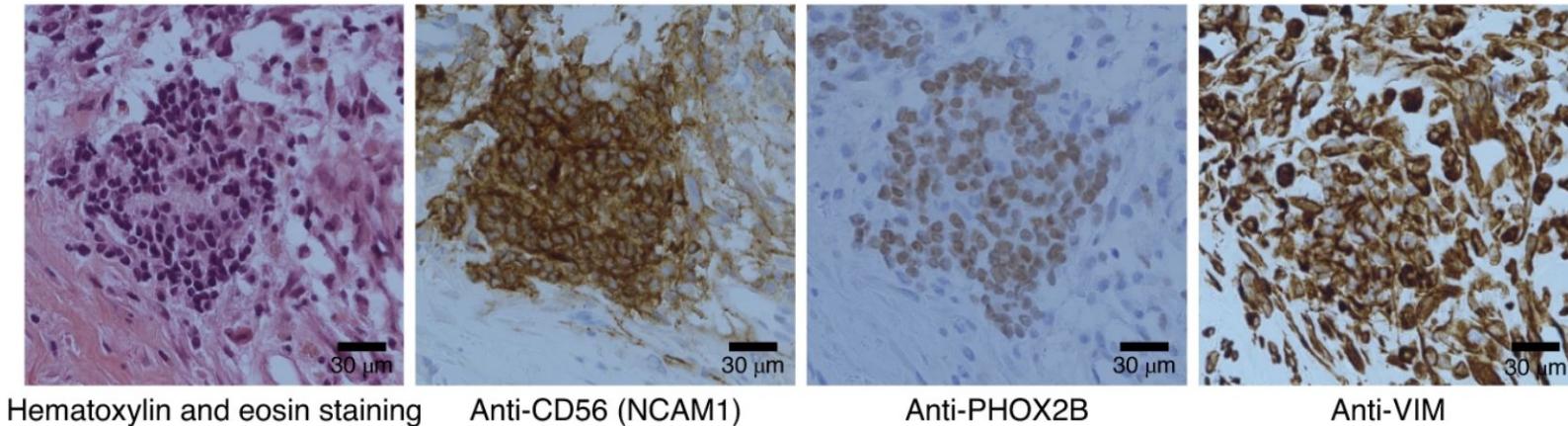
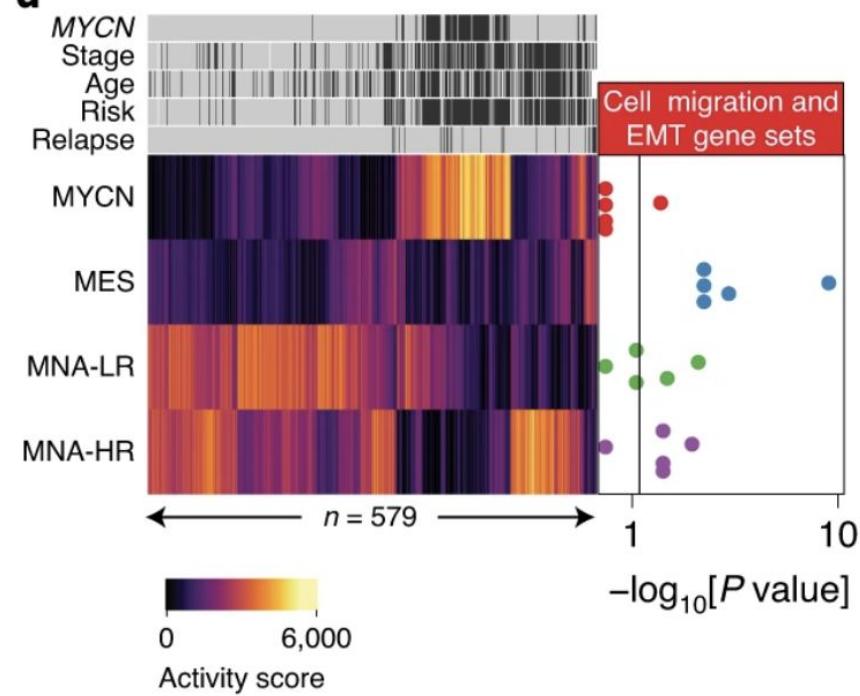
Hopp Children's Cancer Center Heidelberg (KiTZ), Heidelberg, Germany

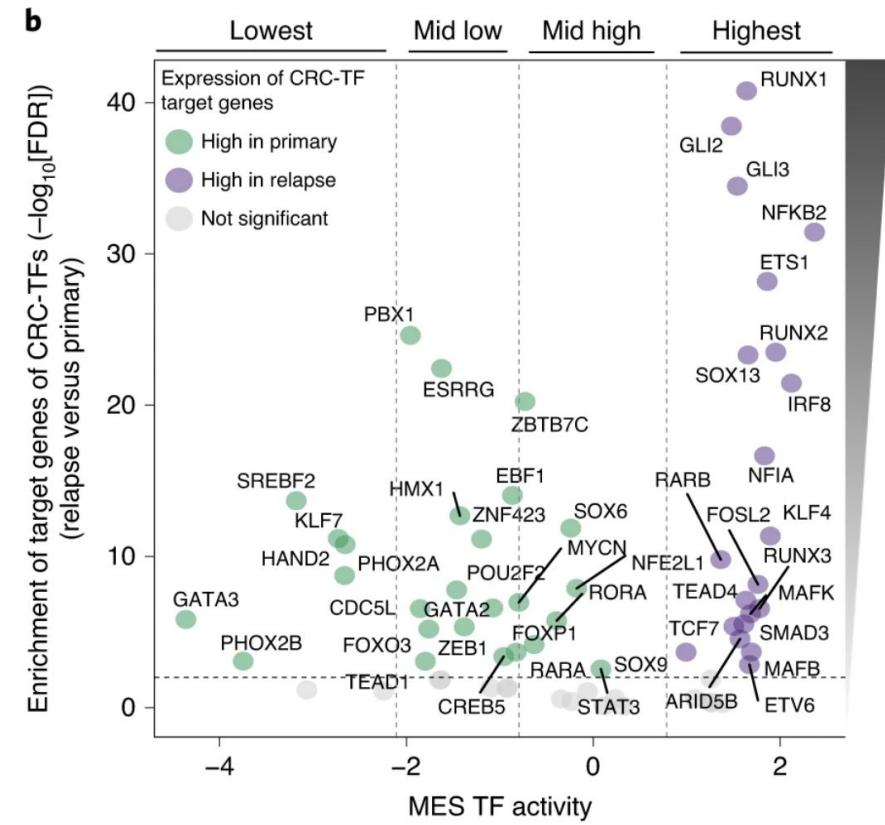
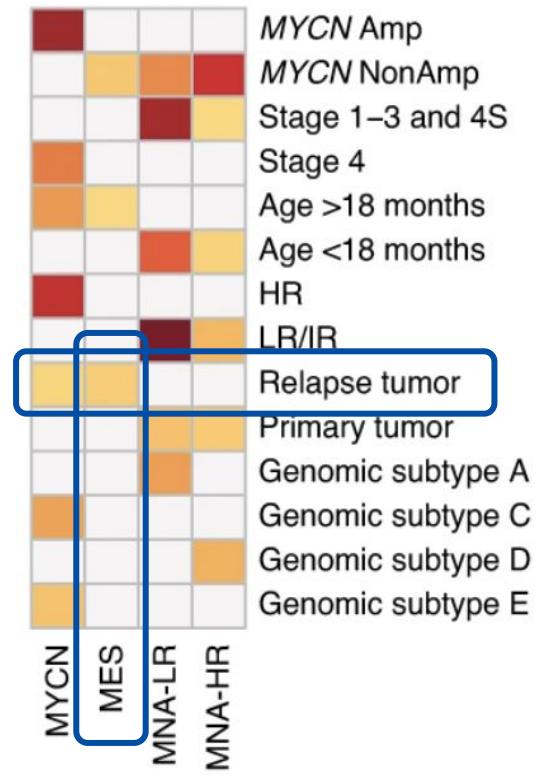
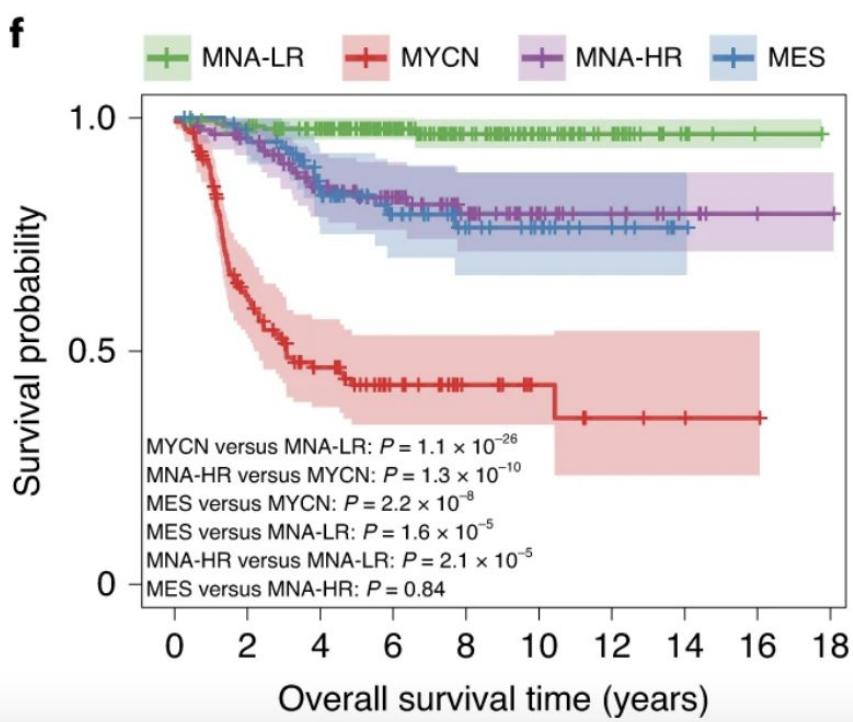
Division of Neuroblastoma Genomics, German Cancer Research Center, Heidelberg,

Germany

<https://doi.org/10.1038/s43018-020-00145-w>

nature cancer

b**d**



Computational methods of **unsupervised** cell type enumeration can identify clinically and biologically relevant disease subtypes

Single cell guided deconvolution

CIBERSORTx (CSx)

Determining cell type abundance and expression from bulk tissues with digital cytometry

Aaron M. Newman , Chloé B. Steen, Chih Long Liu, Andrew J. Gentles, Aadel A. Chaudhuri, Florian Scherer, Michael S. Khodadoust, Mohammad S. Esfahani, Bogdan A. Luca, David Steiner, Maximilian Diehn & Ash A. Alizadeh 

Nature Biotechnology **37**, 773–782(2019) | [Cite this article](#)

39k Accesses | **160** Citations | **140** Altmetric | [Metrics](#)

Cell Population Mapping (CPM)

Article | Published: 18 March 2019

Cell composition analysis of bulk genomics using single-cell data

Amit Frishberg, Naama Peshes-Yaloz, Ofir Cohn, Diana Rosenthal, Yael Steuerman, Liran Valadarsky, Gal Yankovitz, Michal Mandelboim, Fuad A. Iraqi, Ido Amit, Lior Mayo, Eran Bacharach  & Irit Gat-Viks 

Nature Methods **16**, 327–332(2019) | [Cite this article](#)

12k Accesses | **22** Citations | **69** Altmetric | [Metrics](#)

Multi-subject Single Cell deconvolution (MuSiC)

Article | [Open Access](#) | Published: 22 January 2019

Bulk tissue cell type deconvolution with multi-subject single-cell expression reference

Xuran Wang, Jihwan Park, Katalin Susztak, Nancy R. Zhang  & Mingyao Li 

Nature Communications **10**, Article number: 380 (2019) | [Cite this article](#)

39k Accesses | **77** Citations | **81** Altmetric | [Metrics](#)

Single cell-assisted deconvolutional DNN (Scaden)

Deep learning-based cell composition analysis from tissue expression profiles

 Kevin Menden^{1,*},  Mohamed Marouf²,  Sergio Oller², Anupriya Dalmia¹,  Daniel Sumner Magruder^{2,3}, Karin Kloiber²,  Peter Heutink¹ and  Stefan Bonn^{1,2,*}

¹German Center for Neurodegenerative Diseases, Tuebingen, Germany.

²Institute of Medical Systems Biology, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

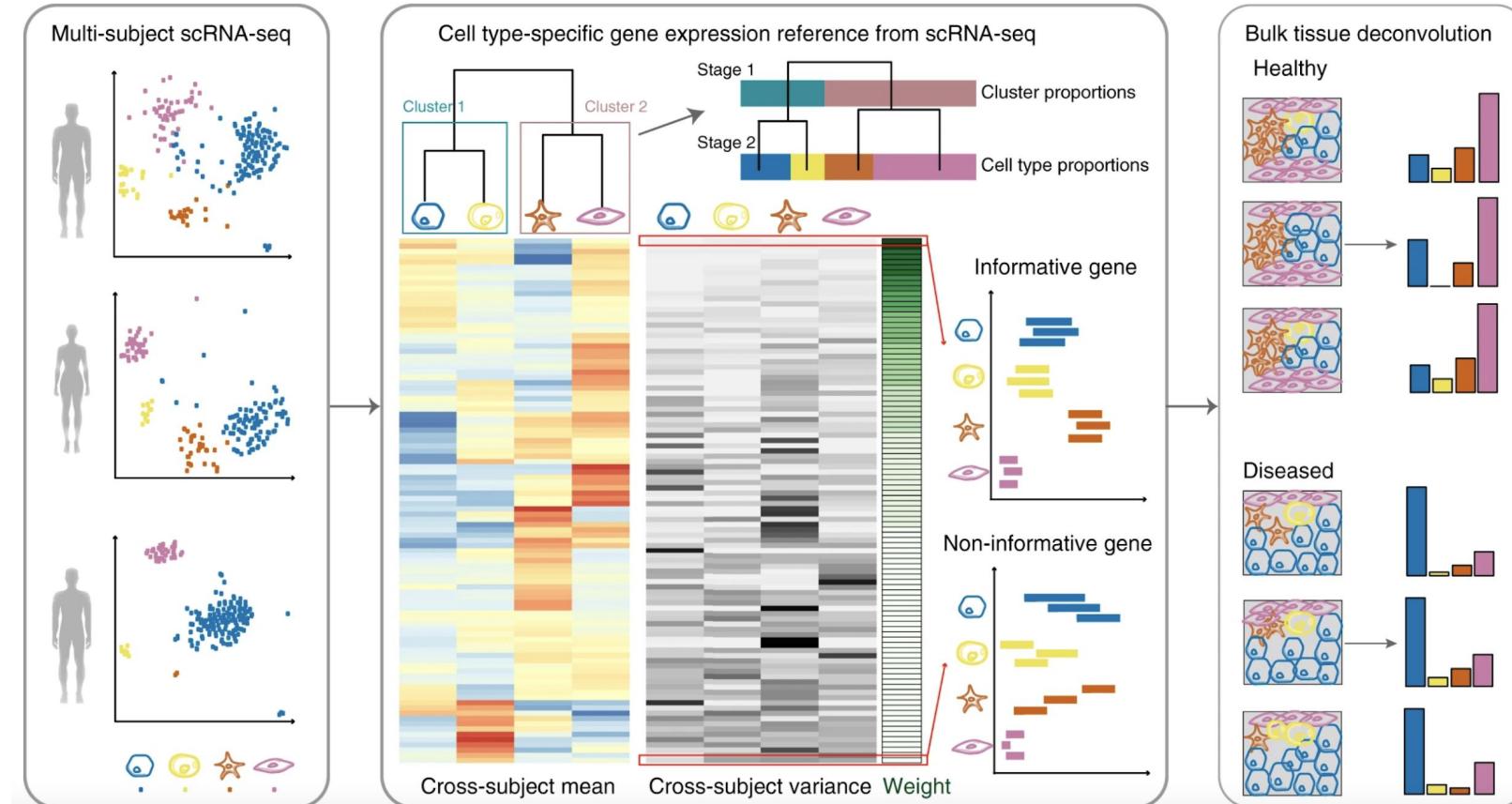
³Genevention GmbH, Goettingen, Germany.

*Corresponding author. Email: sbonn@uke.de (S.B.); kevin.menden@dzne.de (K.M.)

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Science Advances 22 Jul 2020:
Vol. 6, no. 30, eaba2619
DOI: 10.1126/sciadv.eaba2619

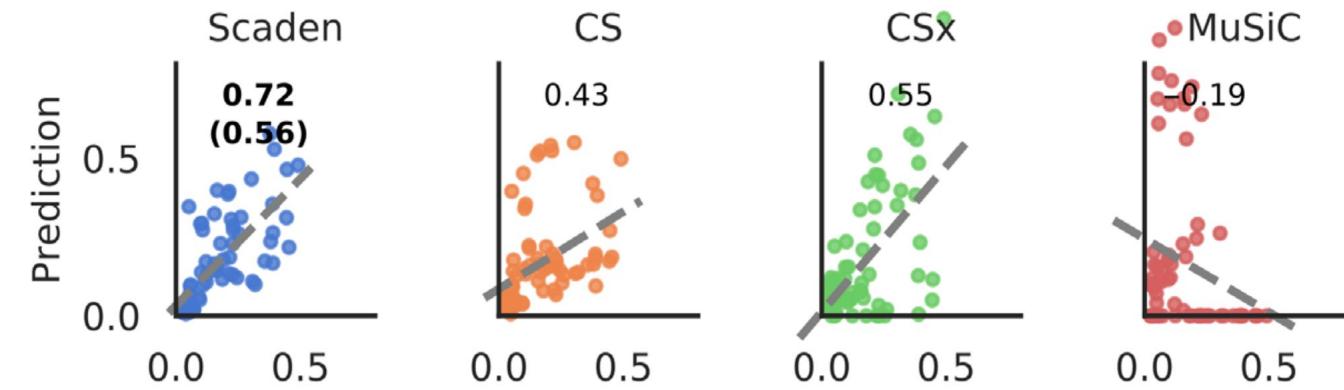
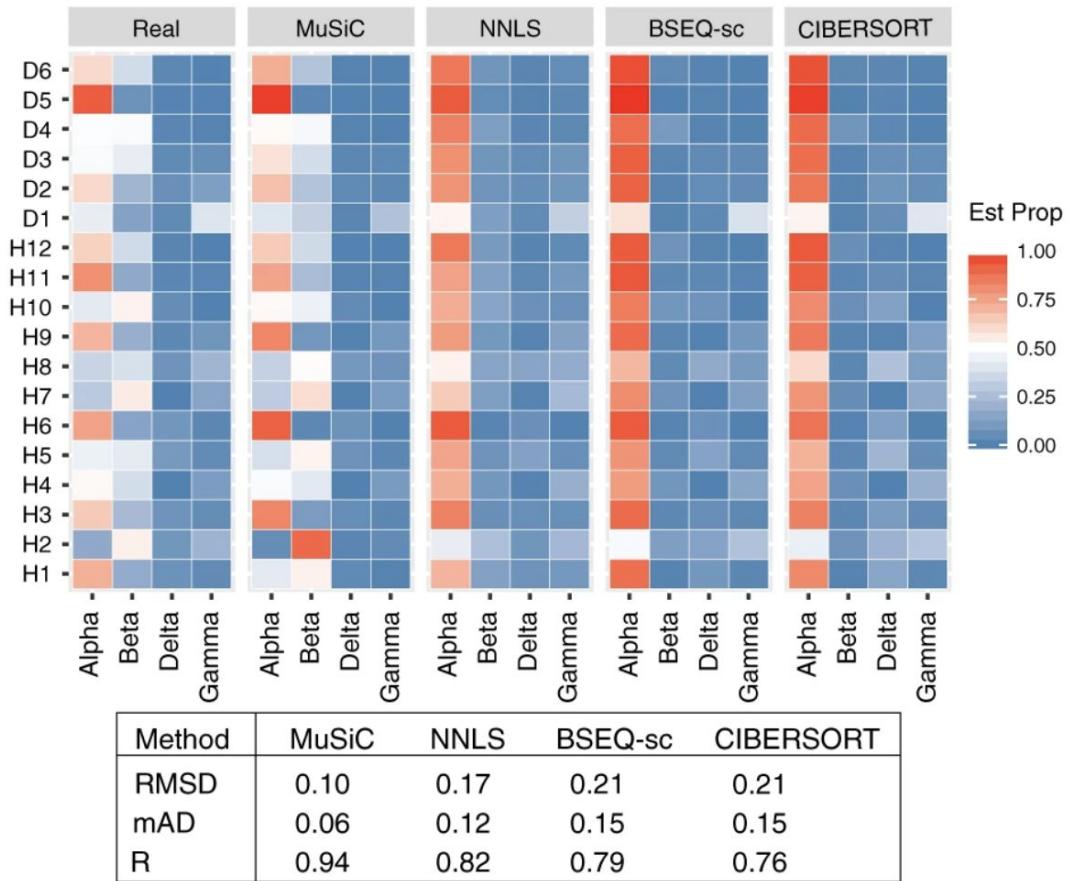
- Do we know all the cell types ?
- Limitations of reference marker genes
- “*You cannot find which you cannot see*”



MuSiC

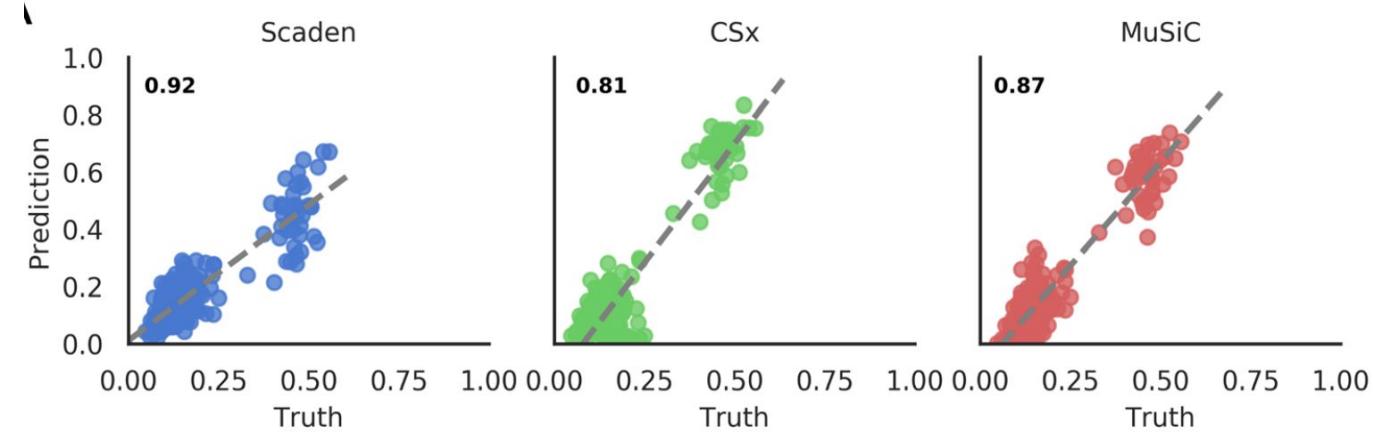
Peripheral Blood mononuclear cells

b



ScaDen

Brain cells





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Yasmina Kermezli, Uni Grenoble Alpes

Magali Richard, Uni Grenoble Alpes

Ashwini Sharma, University Hospital Heidelberg

https://cancer-heterogeneity.github.io/cometh_training.html

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