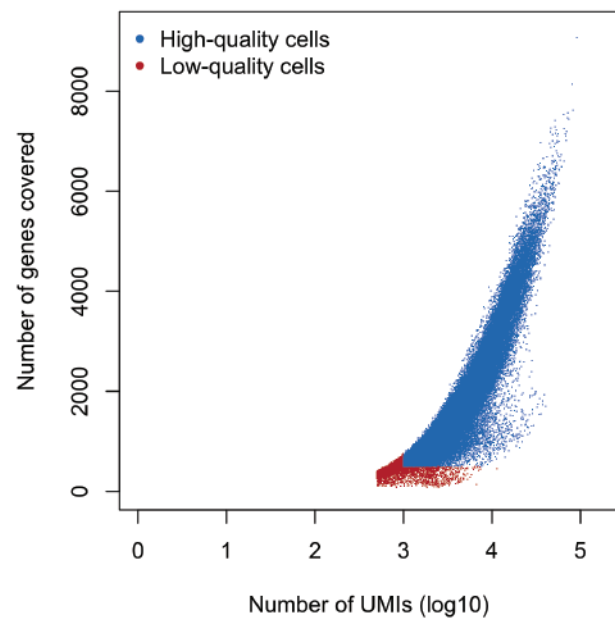
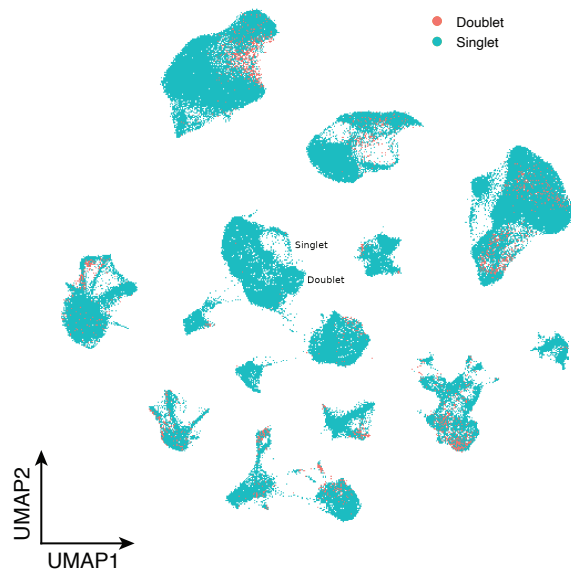


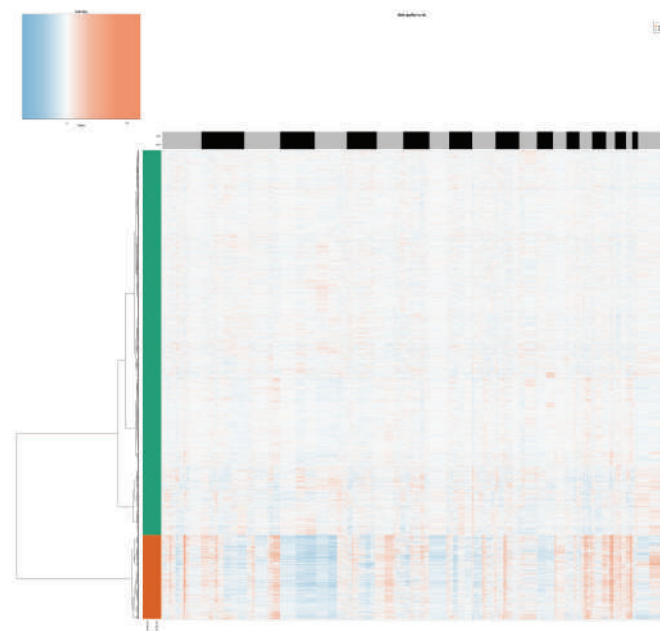
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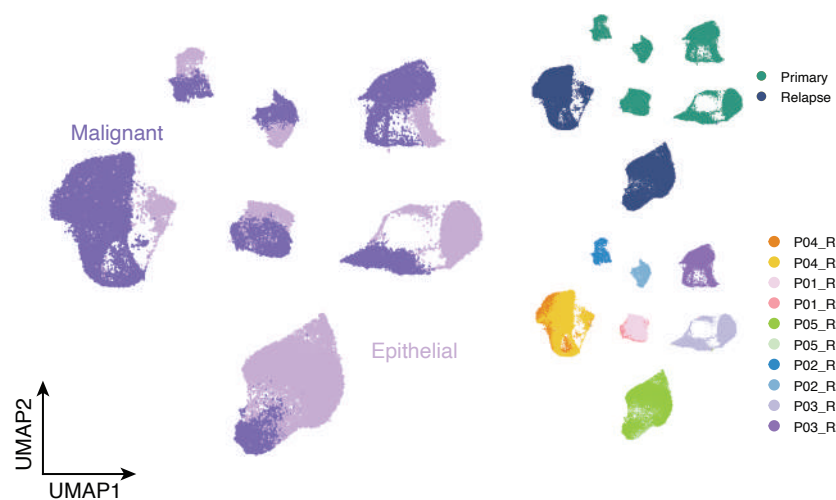
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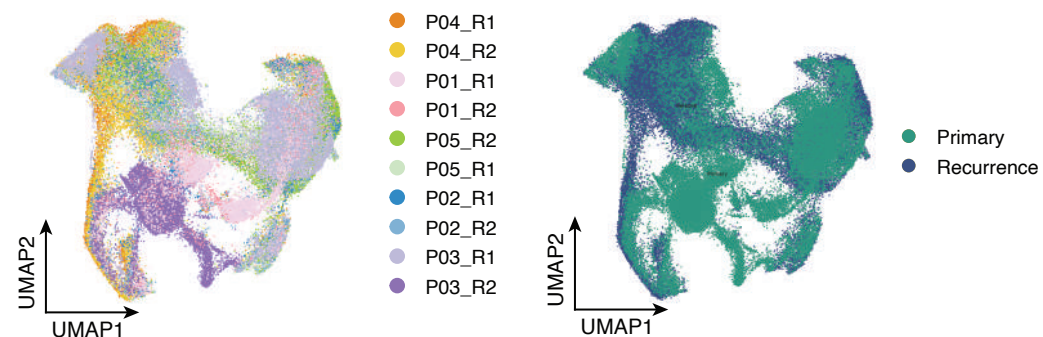
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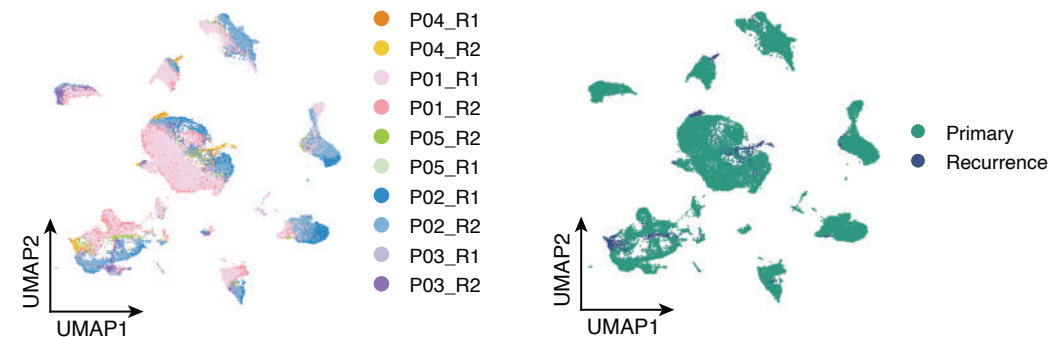
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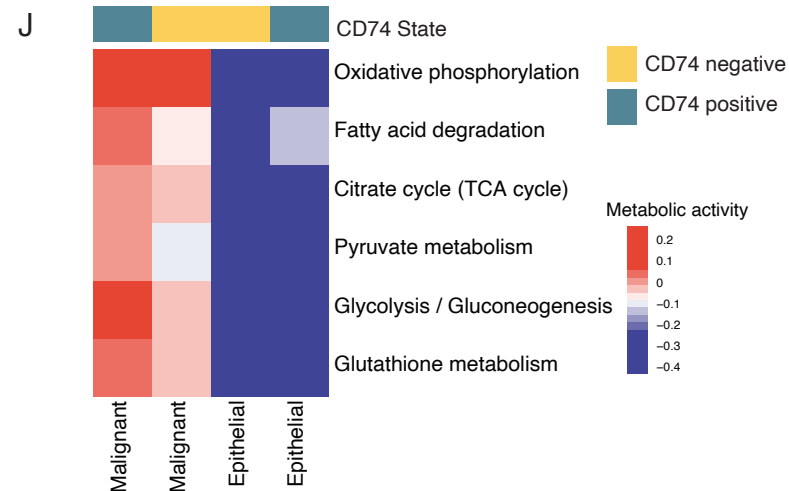
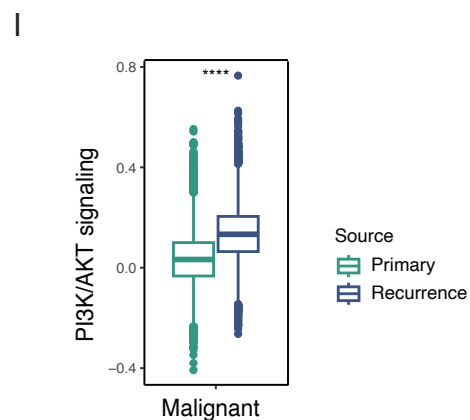
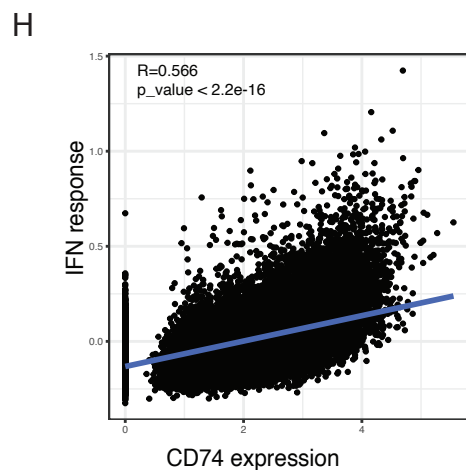
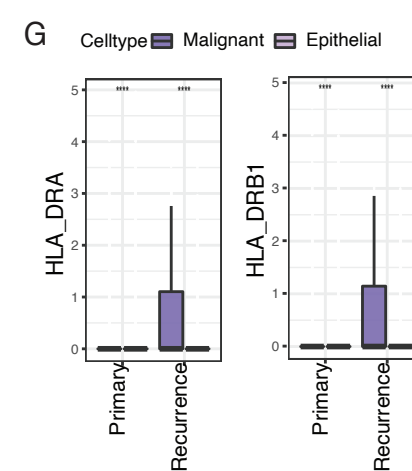
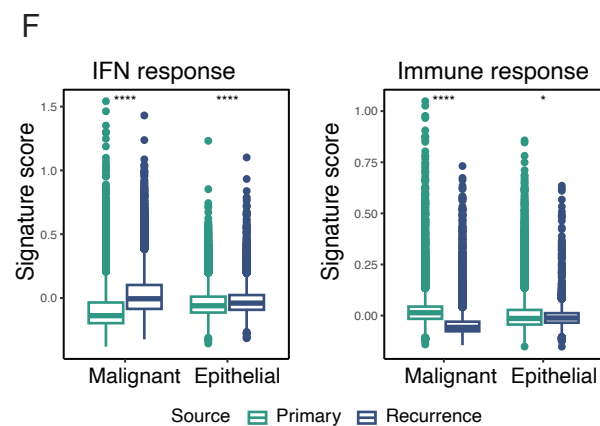
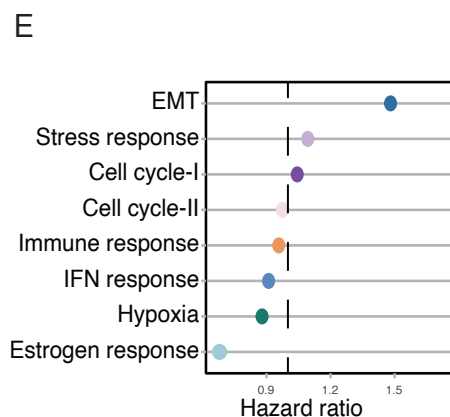
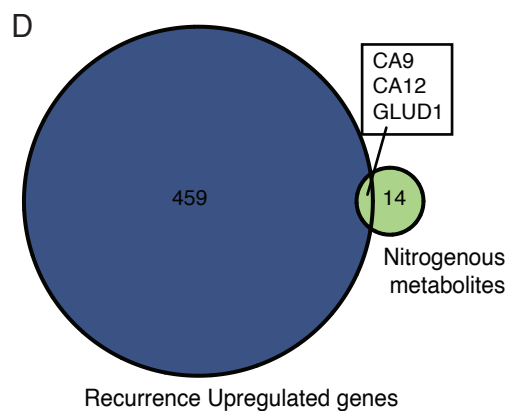
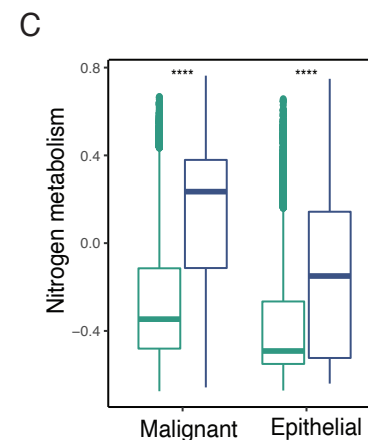
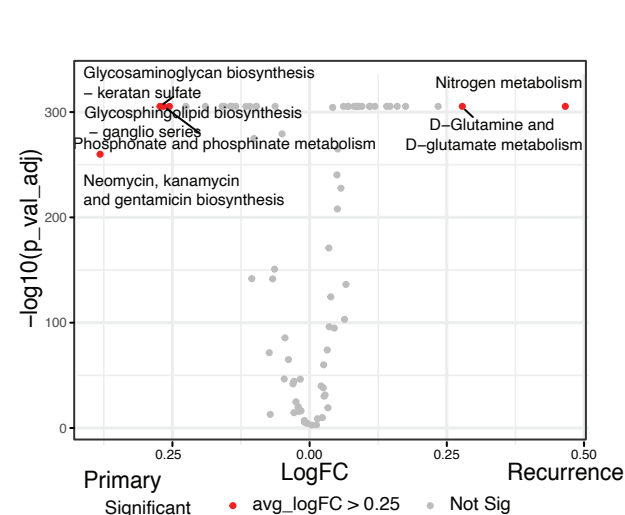
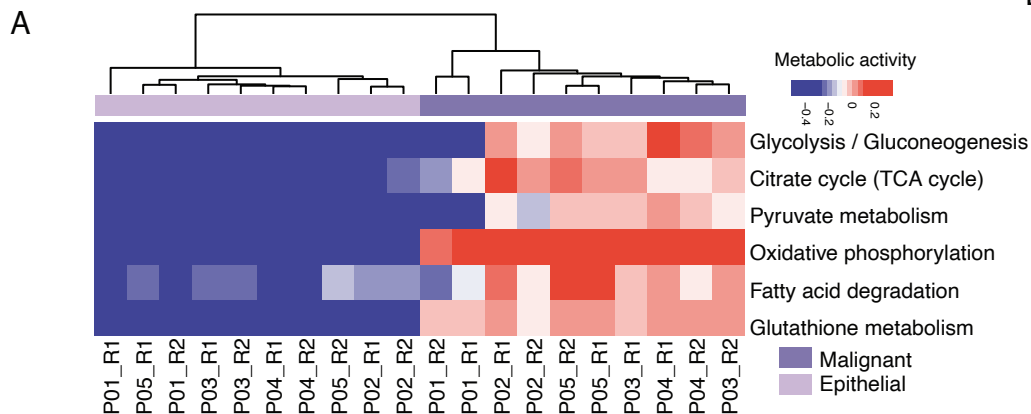


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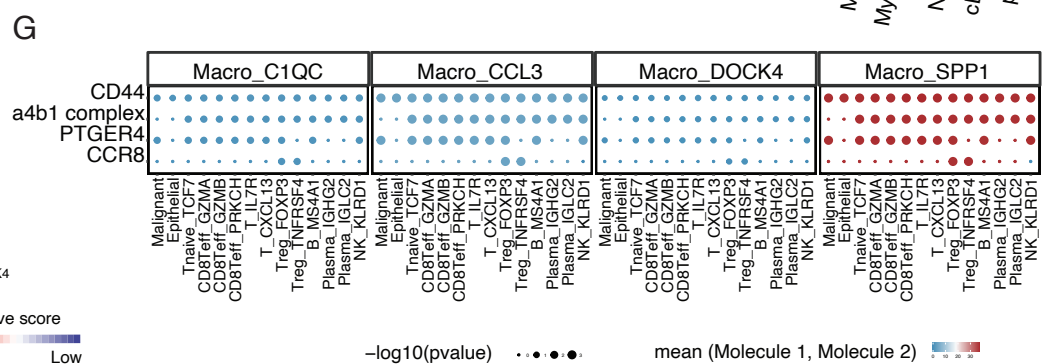
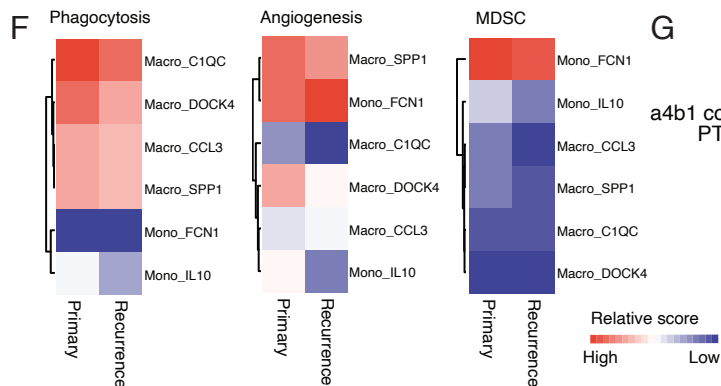
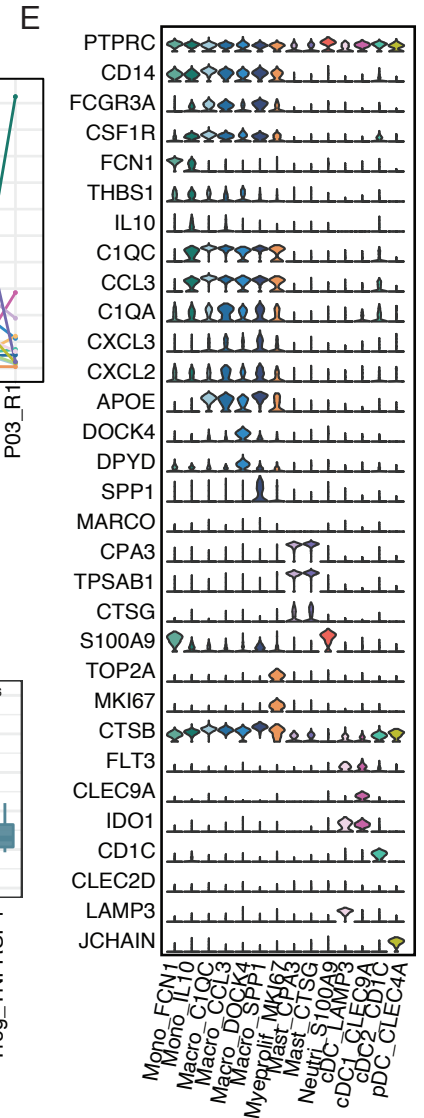
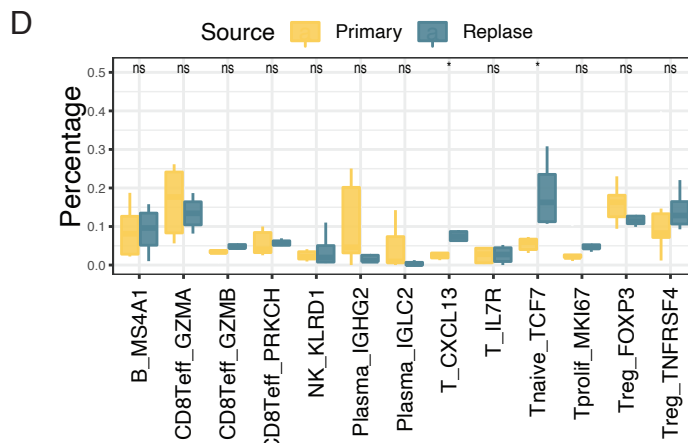
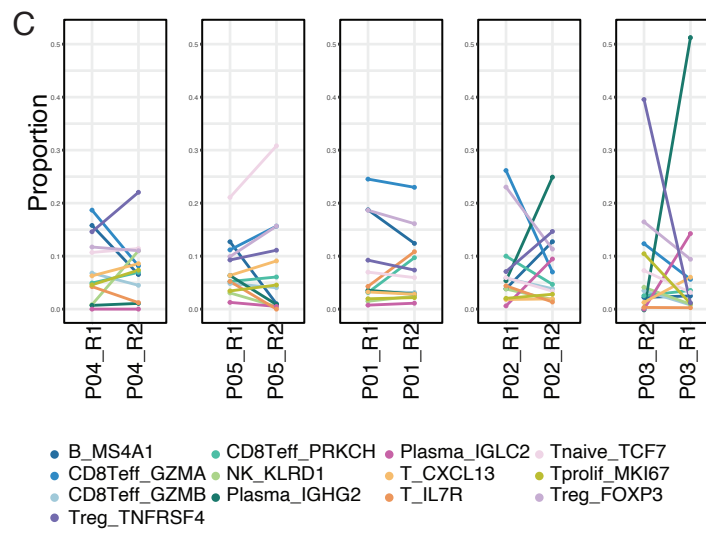
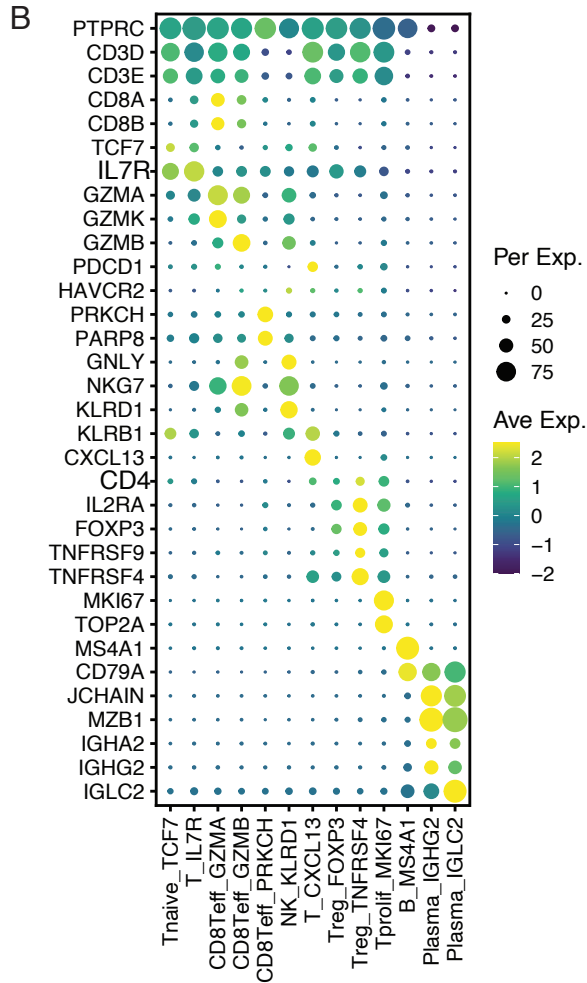
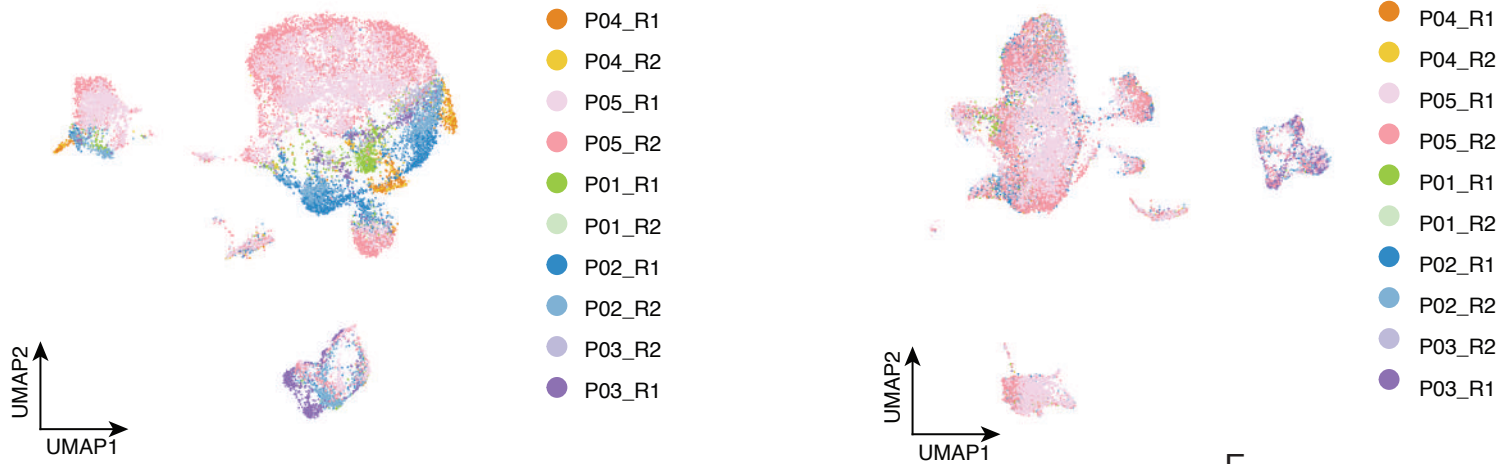
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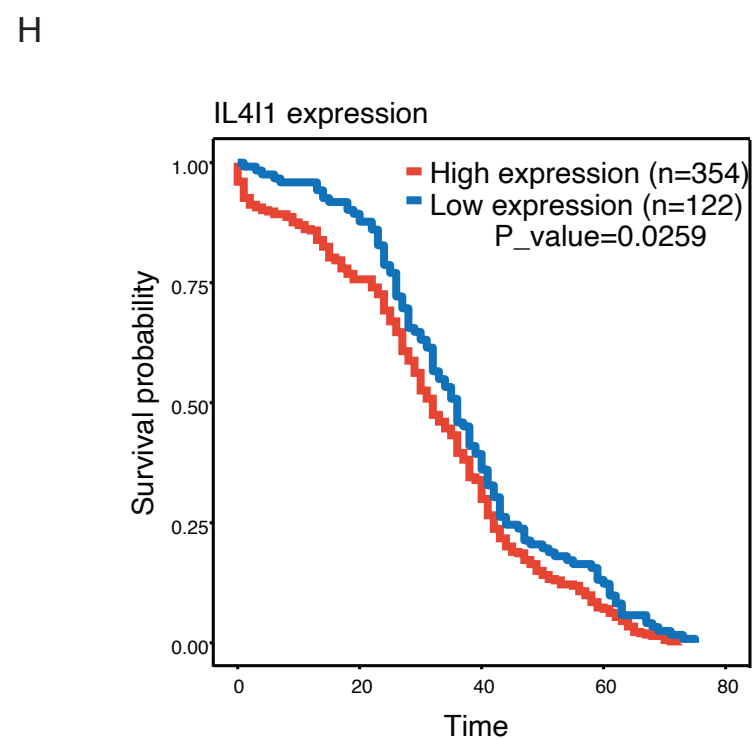
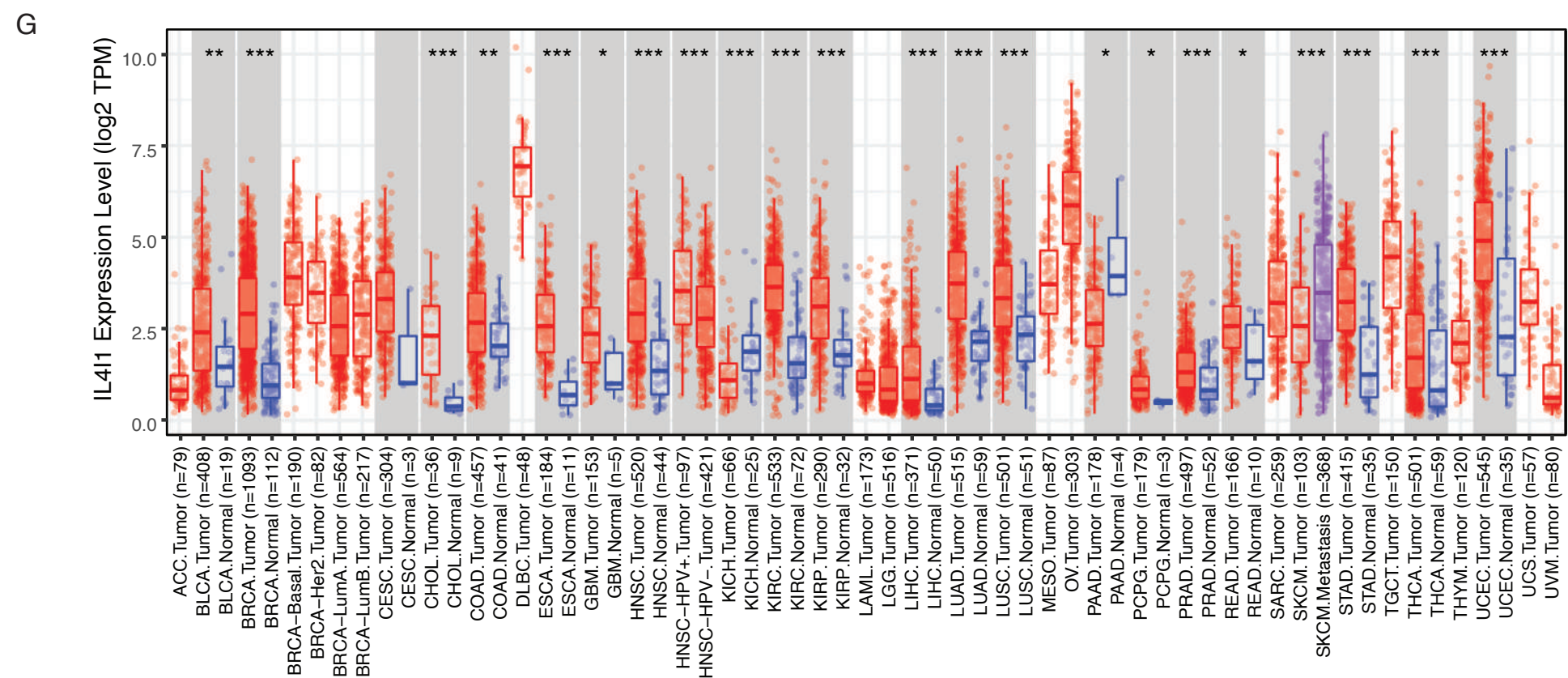
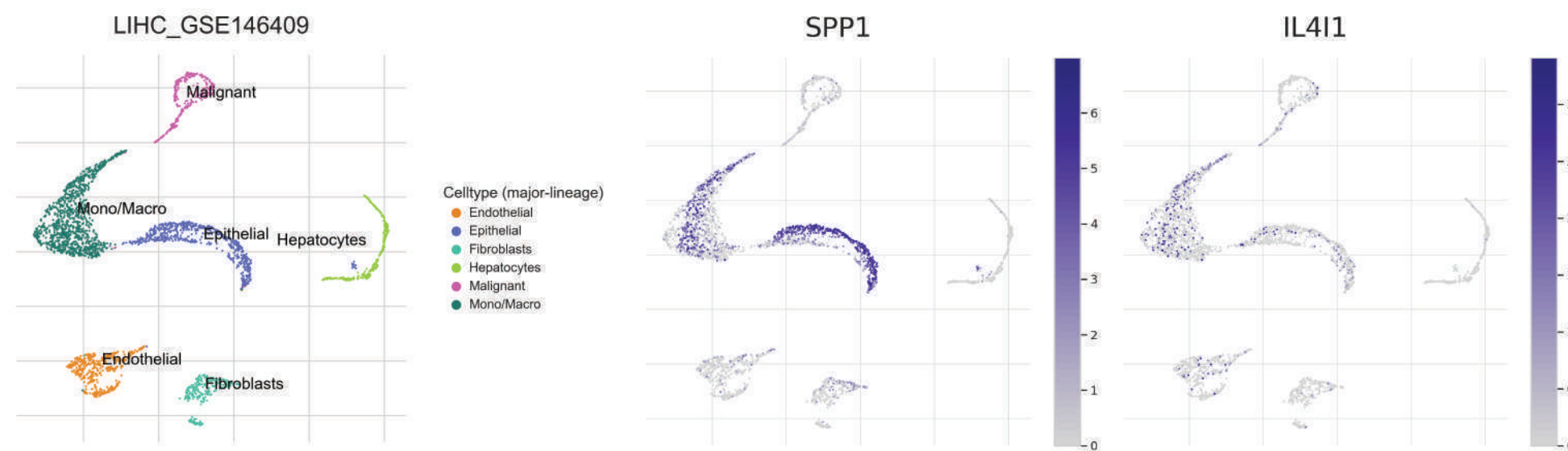
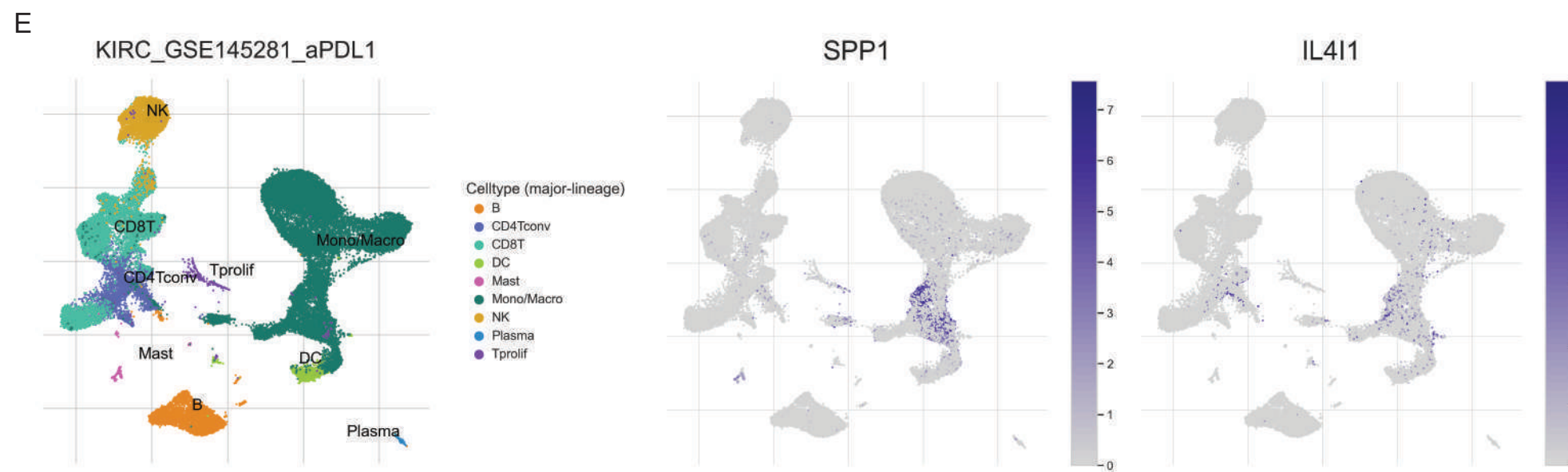
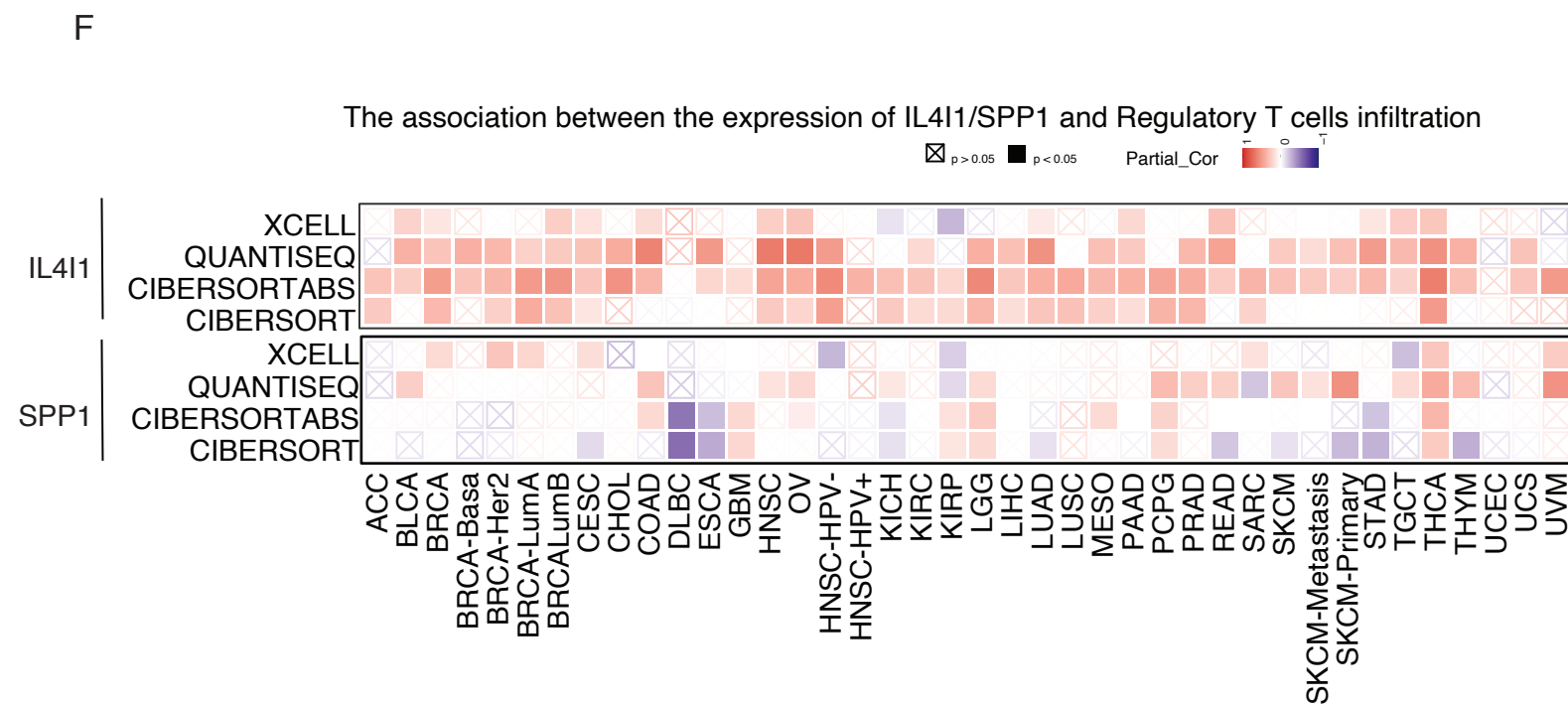
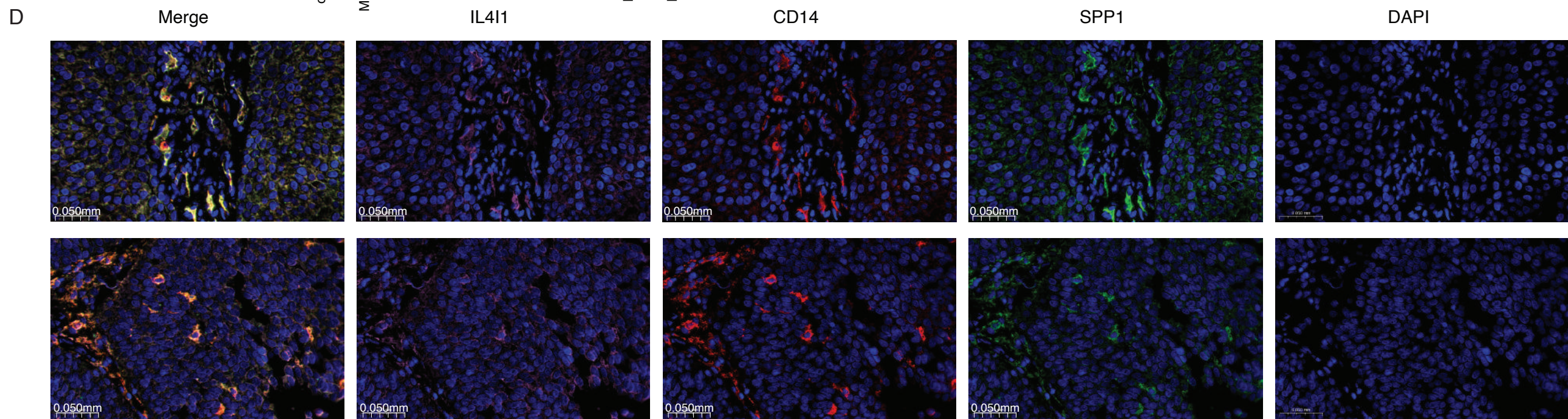
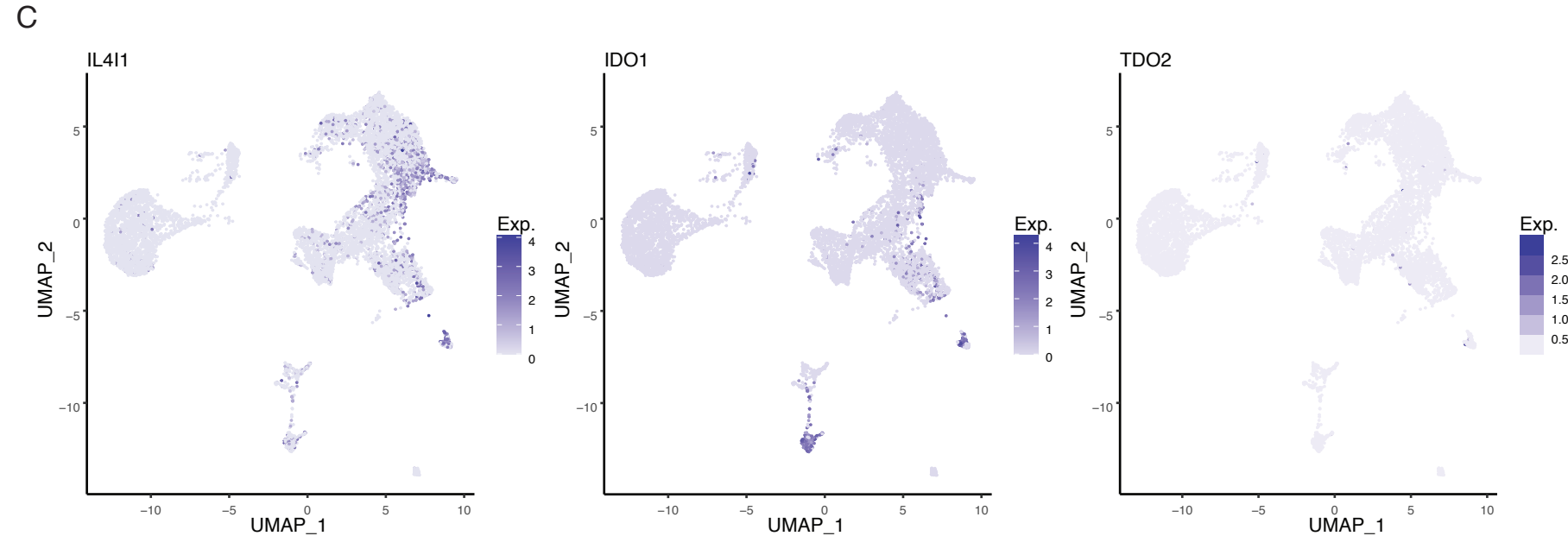
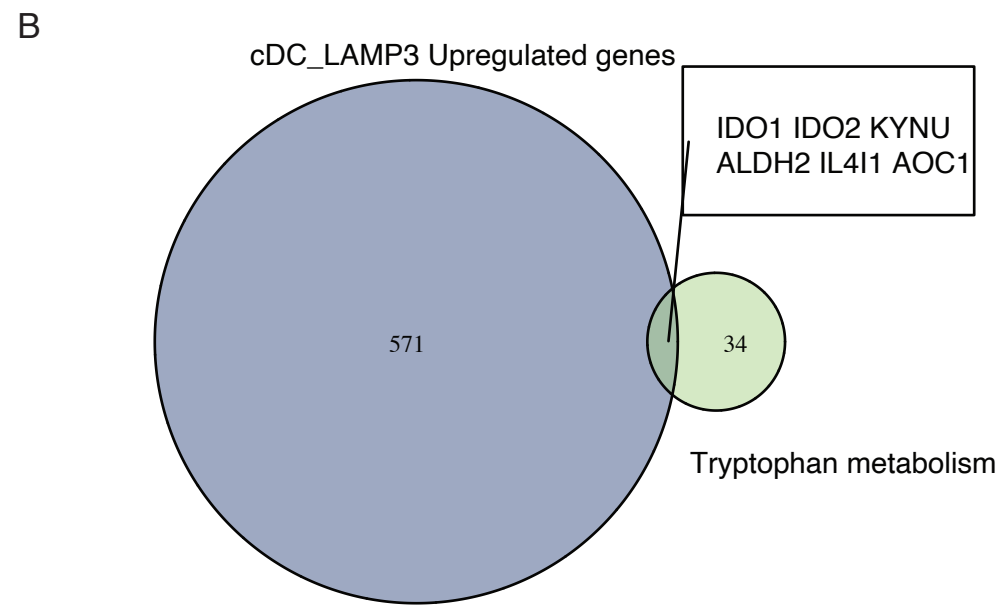
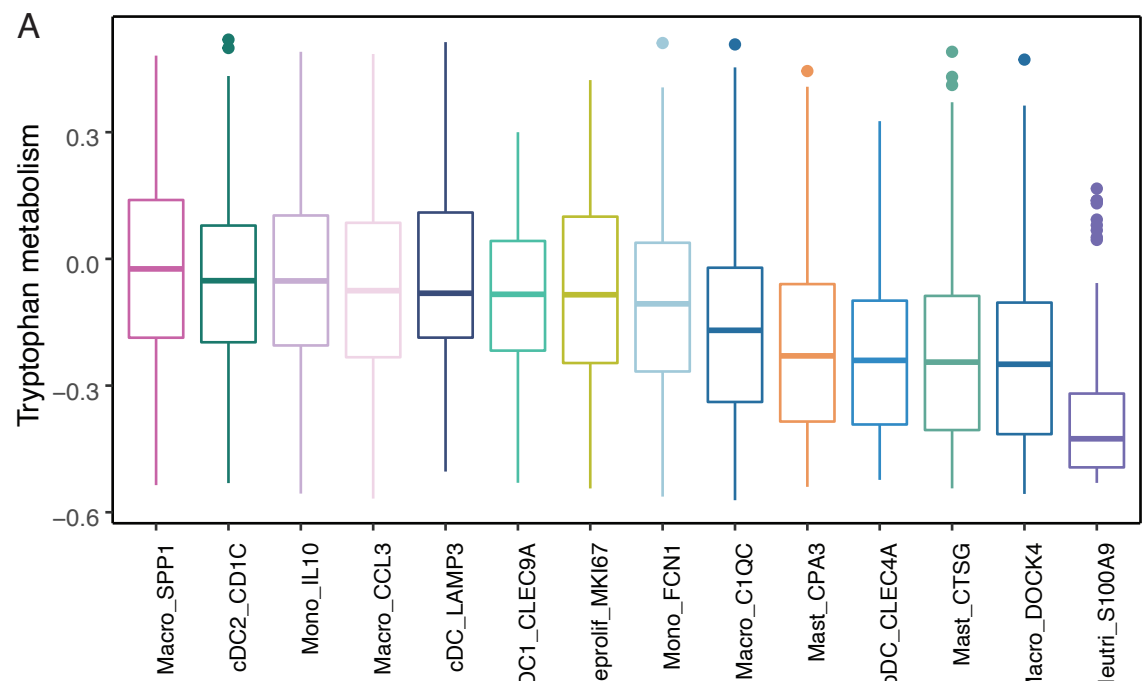




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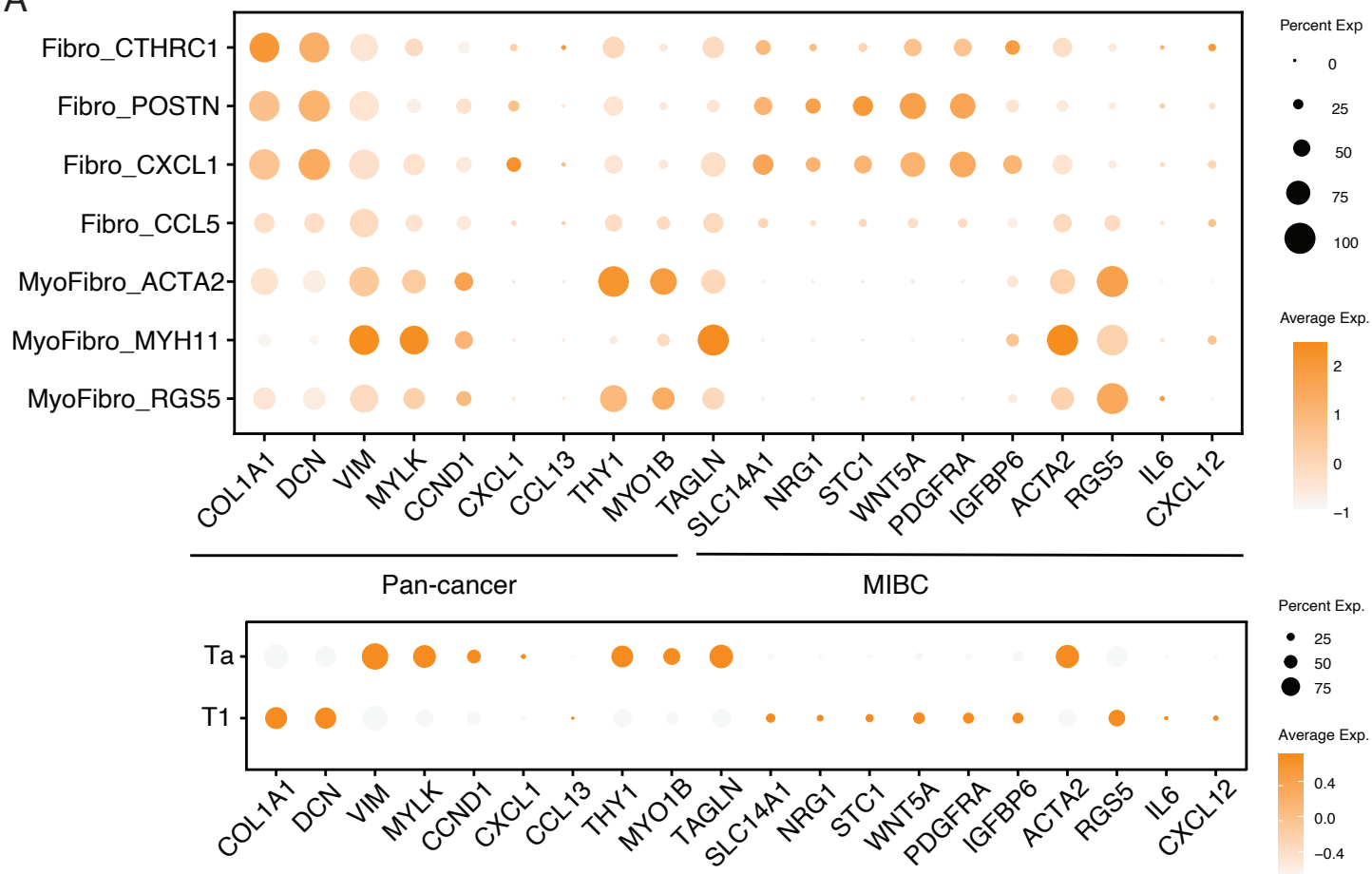




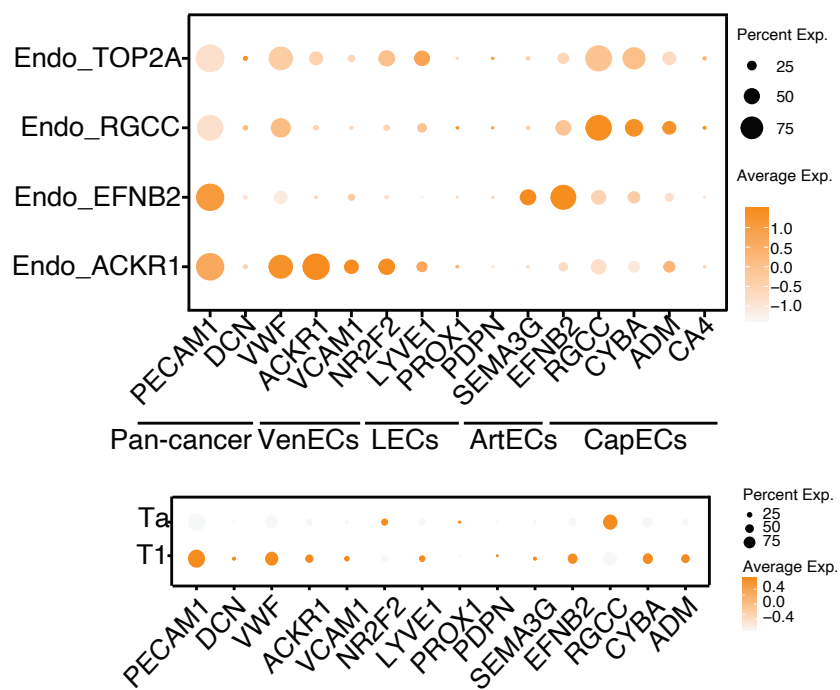




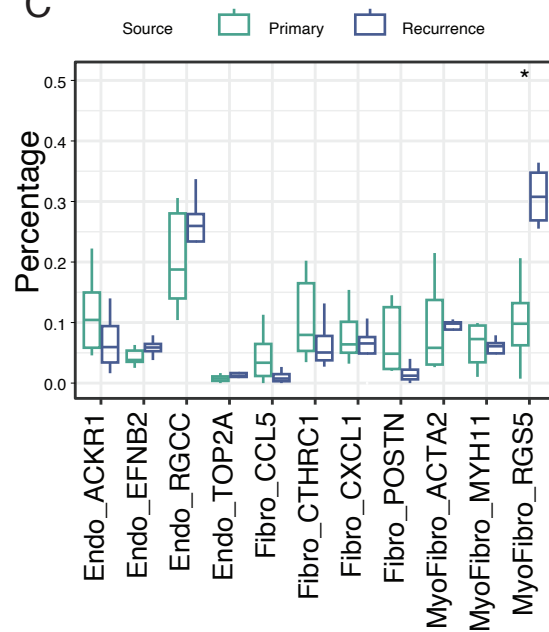
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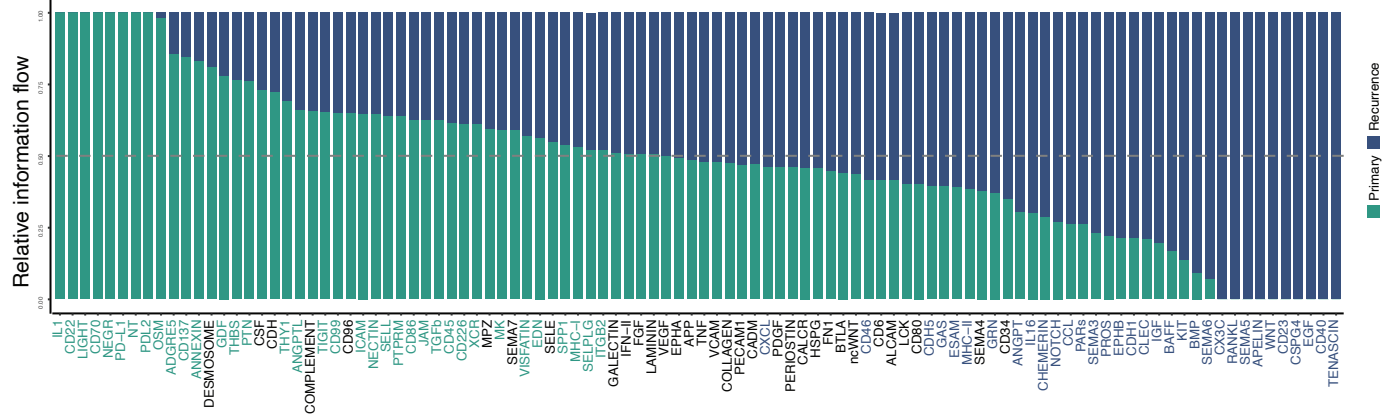
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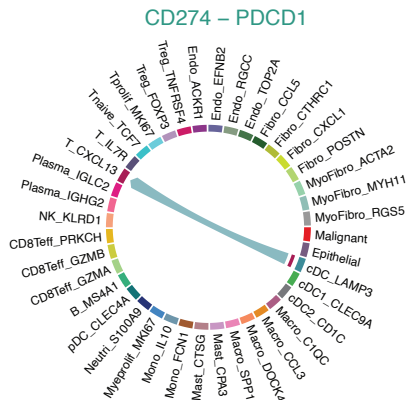
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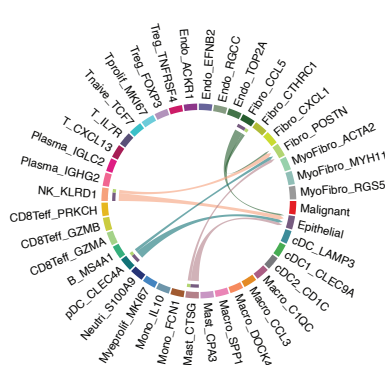
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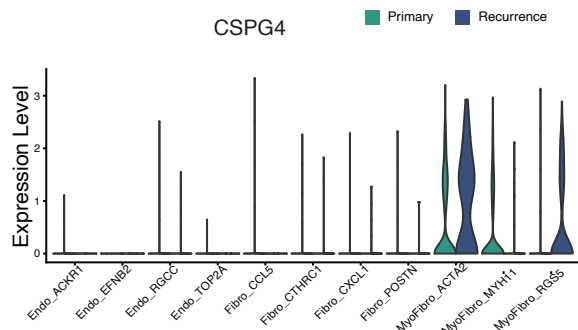
B



## AREG – EGFR



C



TableS1: Clinical\_information.

| PatientID | SampleID | Age | Gender | Height | Weight | Smoking history | Primary/ Relapsed | Tumor site           | Intervesical treatment | T              | N | M | Pathological grade |
|-----------|----------|-----|--------|--------|--------|-----------------|-------------------|----------------------|------------------------|----------------|---|---|--------------------|
| P01       | P01_R1   | 69  | Male   | 175    | 75     | Yes             | Primary           | posterior wall       | Epirubicin             | T1             | 0 | 0 | H                  |
| P01       | P01_R2   | 69  | Male   | 175    | 75     | Yes             | Primary           | left wall            | Epirubicin             | T1             | 0 | 0 | H                  |
| P02       | P02_R1   | 72  | Male   | 160    | 57     | Yes             | Primary           | posterior wall       | None                   | T1/<br>Cl<br>S | 0 | 0 | H                  |
| P02       | P02_R2   | 72  | Male   | 160    | 57     | Yes             | Primary           | left wall            | None                   | T1/<br>Cl<br>S | 0 | 0 | H                  |
| P03       | P03_R1   | 82  | Female | 158    | 48     | None            | Primary           | lower ureter segment | Epirubicin             | T1             | 0 | 0 | H                  |
| P03       | P03_R2   | 82  | Female | 158    | 48     | None            | Primary           | posterior wall       | Epirubicin             | Ta             | 0 | 0 | H                  |
| P04       | P04_R1   | 69  | Male   | 175    | 70     | Yes             | Relapsed          | posterior wall       | None                   | T1             | 0 | 0 | H                  |
| P04       | P04_R2   | 69  | Male   | 175    | 70     | Yes             | Relapsed          | right wall           | None                   | T1             | 0 | 0 | H                  |
| P05       | P05_R1   | 68  | Male   | 176    | 81     | None            | Relapsed          | front wall           | BCG                    | Ta             | 0 | 0 | H                  |
| P05       | P05_R2   | 68  | Male   | 176    | 81     | None            | Relapsed          | right wall           | BCG                    | Ta             | 0 | 0 | H                  |



**Table S2 Signature genes.**

| Signature              | Gene   | Signature         | Gene     | Signature    | Gene     | Signature          | Gene     | Signature                        | Gene    |
|------------------------|--------|-------------------|----------|--------------|----------|--------------------|----------|----------------------------------|---------|
| PI3K/AKT pathway genes | XIAP   | Anti inflammatory | IL1RN    | M2           | MMP 9    | ECM                | PDGFA    | Arterial endothelial cells       | EFNB2   |
| PI3K/AKT pathway genes | AKT1   | Anti inflammatory | IL10     | M2           | CLEC 7A  | ECM                | MMP2     | Capillary-like endothelial cells | RGCC    |
| PI3K/AKT pathway genes | TWIST1 | Anti inflammatory | IL4      | M2           | WNT 7B   | ECM                | COL1A2   | Capillary-like endothelial cells | CYBA    |
| PI3K/AKT pathway genes | BAD    | Anti inflammatory | IL11     | M2           | FASL     | ECM                | RGS5     | Capillary-like endothelial cells | ADM     |
| PI3K/AKT pathway genes | CDKN1A | Anti inflammatory | IL13     | M2           | TNFS F12 | Immune regulatory  | C5       | Capillary-like endothelial cells | CA4     |
| PI3K/AKT pathway genes | ABL1   | Anti inflammatory | TGFB1    | M2           | TNFS F8  | Immune regulatory  | C5AR1    | Pan-cancer fibroblasts           | COL1A1  |
| PI3K/AKT pathway genes | CDH1   | Anti inflammatory | TNFRSF1A | M2           | CD27 6   | Immune regulatory  | TGFB1    | Pan-cancer fibroblasts           | DCN     |
| PI3K/AKT pathway genes | TP53   | Anti inflammatory | TNFRSF1B | M2           | VTC N1   | Immune regulatory  | TGFBR1   | Pan-cancer fibroblasts           | VIM     |
| PI3K/AKT pathway genes | CASP3  | Anti inflammatory | IL1R2    | M2           | MSR 1    | Immune regulatory  | TGFBR2   | Pan-cancer fibroblasts           | MYLK    |
| PI3K/AKT pathway genes | PAK1   | Anti inflammatory | IL18BP   | M2           | FN1      | Immune regulatory  | TGFBR1   | Pan-cancer fibroblasts           | CCND1   |
| PI3K/AKT pathway genes | GAPDH  | Pro inflammatory  | IL1B     | M2           | IRF4     | Immune regulatory  | CXCL12   | Pan-cancer fibroblasts           | CD73    |
| PI3K/AKT pathway genes | PIK3CA | Pro inflammatory  | TNF      | Angiogenesis | CCN D2   | Immune regulatory  | CXCR4    | Pan-cancer fibroblasts           | CXCL1   |
| PI3K/AKT pathway genes | FAS    | Pro inflammatory  | CCL2     | Angiogenesis | CCN E1   | Immune regulatory  | CXCL13   | Pan-cancer fibroblasts           | CCL13   |
| PI3K/AKT pathway genes | AKT2   | Pro inflammatory  | CCL3     | Angiogenesis | CD44     | Immune regulatory  | CXCR5    | Pan-cancer fibroblasts           | THY1    |
| PI3K/AKT pathway genes | FRAP1  | Pro inflammatory  | CCL5     | Angiogenesis | CXC R4   | Immune regulatory  | C7       | Pan-cancer fibroblasts           | MYO1B   |
| PI3K/AKT pathway genes | FOXO1A | Pro inflammatory  | CCL7     | Angiogenesis | E2F3     | Immune regulatory  | CFB      | Pan-cancer fibroblasts           | TAGLN   |
| PI3K/AKT pathway genes | PTK2   | Pro inflammatory  | CCL8     | Angiogenesis | EDN1     | Immune regulatory  | CFH      | MIBC fibroblasts                 | SLC14A1 |
| PI3K/AKT pathway genes | CASP9  | Pro inflammatory  | CCL13    | Angiogenesis | EZH2     | Immune regulatory  | CFI      | MIBC fibroblasts                 | NRG1    |
| PI3K/AKT pathway genes | PTEN   | Pro inflammatory  | CCL17    | Angiogenesis | FGF1 8   | Immune regulatory  | BCAM     | MIBC fibroblasts                 | STC1    |
| PI3K/AKT pathway genes | CCND1  | Pro inflammatory  | CCL22    | Angiogenesis | FGF R1   | Immune regulatory  | F11R     | MIBC fibroblasts                 | WNT5A   |
| PI3K/AKT pathway genes | NFKB1  | M1                | IL23     | Angiogenesis | FYN      | Immune regulatory  | IRF5     | MIBC fibroblasts                 | PDGFRA  |
| PI3K/AKT pathway genes | GSK3B  | M1                | TNF      | Angiogenesis | HEY1     | Immune regulatory  | CCL2     | MIBC fibroblasts                 | IGFBP6  |
| PI3K/AKT pathway genes | MDM2   | M1                | CXCL9    | Angiogenesis | ITGA V   | Immune regulatory  | IL6      | MIBC fibroblasts                 | ACTA2   |
| PI3K/AKT pathway genes | CDKN1B | M1                | CXCL10   | Angiogenesis | JAG1     | Immune regulatory  | CXCL2    | MIBC fibroblasts                 | RGS5    |
| Cytotoxicity           | PRF1   | M1                | CXCL11   | Angiogenesis | JAG2     | Immune regulatory  | CXCL1    | MIBC fibroblasts                 | IL6     |
| Cytotoxicity           | IFNG   | M1                | CD86     | Angiogenesis | MMP 9    | Immune regulatory  | CXCL3    | MIBC fibroblasts                 | CXCL12  |
| Cytotoxicity           | GNLY   | M1                | IL1A     | Angiogenesis | NOT CH1  | Antigen presenting | CD74     |                                  |         |
| Cytotoxicity           | NKG7   | M1                | IL1B     | Angiogenesis | PDG FA   | Antigen presenting | HLA-DQA1 |                                  |         |
| Cytotoxicity           | GZMB   | M1                | IL6      | Angiogenesis | PTK2     | Antigen presenting | CD83     |                                  |         |
| Cytotoxicity           | GZMA   | M1                | CCL5     | Angiogenesis | SPP1     | Antigen presenting | HLA-DRA  |                                  |         |
| Cytotoxicity           | GZMH   | M1                | IRF5     | Angiogenesis | STC1     | Antigen presenting | HLA-DPA1 |                                  |         |
| Cytotoxicity           | KLRK1  | M1                | IRF1     | Angiogenesis | TNFA IP6 | Antigen presenting | HLA-DQA  |                                  |         |
| Cytotoxicity           | KLRB1  | M1                | CD40     | Angiogenesis | TYM P    | Antigen presenting | CD74     |                                  |         |
| Cytotoxicity           | KLRD1  | M1                | IDO1     | Angiogenesis | VAV2     | Antigen presenting | HLA-DRA  |                                  |         |
| Cytotoxicity           | CTSW   | M1                | KYNU     | Angiogenesis | VCA N    | Antigen presenting | HLA-DRB1 |                                  |         |
| Cytotoxicity           | CST7   | M1                | CCR7     | Angiogenesis | VEG FA   | Antigen presenting | H2-Q4    |                                  |         |
| Cytotoxicity           | CCL4   | M2                | IL4R     | ECM          | ACTA 2   | Tip                | ANGPT2   |                                  |         |
| Cytotoxicity           | CCL3   | M2                | CCL4     | ECM          | TAGL N   | Tip                | APLN     |                                  |         |

|              |         |    |       |     |         |                              |         |  |  |
|--------------|---------|----|-------|-----|---------|------------------------------|---------|--|--|
| Exhausted    | PDCD1   | M2 | CCL13 | ECM | BGN     | Tip                          | FSCN1   |  |  |
| Exhausted    | CTLA4   | M2 | CCL20 | ECM | COL8A1  | Tip                          | PGF     |  |  |
| Exhausted    | LAG3    | M2 | CCL17 | ECM | COL15A1 | Tip                          | PLXND1  |  |  |
| Exhausted    | HAVCR2  | M2 | CCL18 | ECM | IGFBP7  | Tip                          | ADM     |  |  |
| Exhausted    | CD244   | M2 | CCL22 | ECM | TPM1    | Tip                          | PDGFB   |  |  |
| Exhausted    | CD160   | M2 | CCL24 | ECM | TPM2    | Tip                          | CXCR4   |  |  |
| Exhausted    | TIGIT   | M2 | LYVE1 | ECM | COL10A1 | Tip                          | ESM1    |  |  |
| Regulatory   | IL2RA   | M2 | VEGFA | ECM | POSTN   | Tip                          | PXDN    |  |  |
| Regulatory   | IL1R2   | M2 | VEGFB | ECM | MYL9    | Tip                          | LXN     |  |  |
| Regulatory   | FOXP3   | M2 | VEGFC | ECM | COL13A1 | Tip                          | ANGPTL2 |  |  |
| Regulatory   | LAYN    | M2 | VEGFD | ECM | COL14A1 | Tip                          | INSR    |  |  |
| Regulatory   | TNFRSF9 | M2 | EGF   | ECM | MYH11   | Pan-cancer endothelial cells | PECAM1  |  |  |
| Regulatory   | FANK1   | M2 | CTSA  | ECM | MYLK    | Pan-cancer endothelial cells | DCN     |  |  |
| Regulatory   | RTKN2   | M2 | CTSB  | ECM | ACTG2   | Pan-cancer endothelial cells | VWF     |  |  |
| Regulatory   | IL1R1   | M2 | CTSC  | ECM | FN1     | Venous endothelial cells     | ACKR1   |  |  |
| Regulatory   | CUL9    | M2 | CTSD  | ECM | LUM     | Venous endothelial cells     | VCAM1   |  |  |
| Regulatory   | IKZF2   | M2 | TGFB1 | ECM | DCN     | Venous endothelial cells     | NR2F2   |  |  |
| Phagocytosis | MRC1    | M2 | TGFB2 | ECM | VCAN    | Lymphatic endothelial cells  | LYVE1   |  |  |
| Phagocytosis | CD163   | M2 | TGFB3 | ECM | COL5A1  | Lymphatic endothelial cells  | PROX1   |  |  |
| Phagocytosis | MERTK   | M2 | MMP14 | ECM | COL5A2  | Lymphatic endothelial cells  | PDPN    |  |  |
| Phagocytosis | C1QB    | M2 | MMP19 | ECM | COL63A  | Arterial endothelial cells   | SEMA3G  |  |  |