

## Supplementary Materials for

### **Functional Network Pipeline Reveals Genetic Determinants Associated with in Situ Lymphocyte Proliferation and Survival of Cancer Patients**

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## Supplementary Figure 1

### Cell types expressing *IL15*.

*IL15*, *IL15RA* and *IL2RB* expression level in purified immune cells and in cancer cell lines. 16 immune cell subtypes from the immunome collection (Immunome, Bindea *et al.*, 2013) are shown. 174 cell lines from 9 cancer types were analyzed (Gene Expression Omnibus, GSE32474, Pfister *et al.*, 2009).

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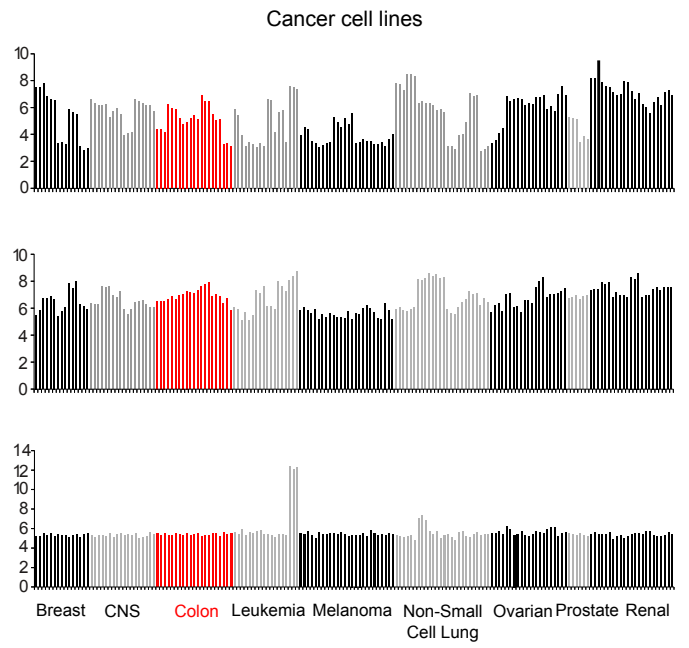
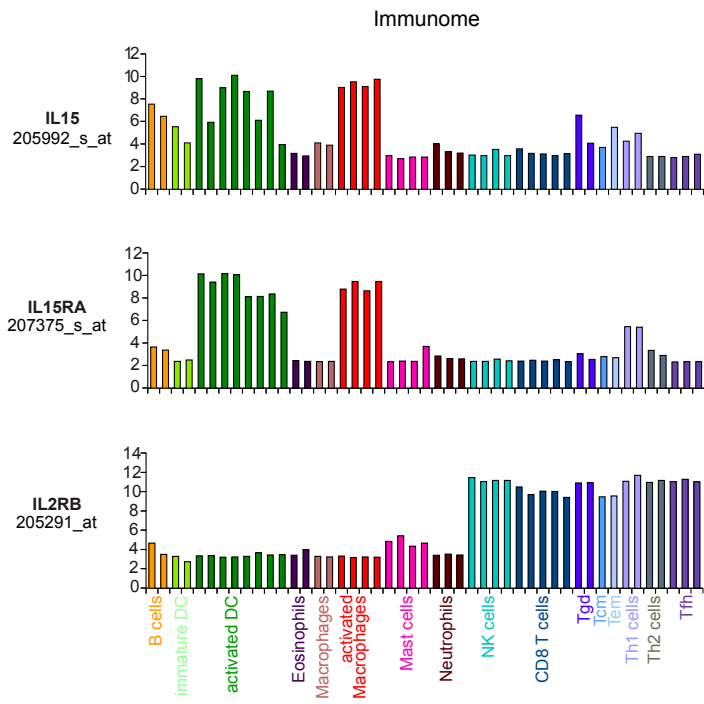
Parkinson, H., *et al.*, (2007). ArrayExpress--a public database of microarray experiments and gene expression profiles. *Nucleic Acids Res* 35, D747-750. Pfister TD *et al.* Topoisomerase I levels in the NCI-60 cancer cell line panel determined by validated ELISA and microarray analysis and correlation with indenoisoquinoline sensitivity. *Mol Cancer Ther* 2009 Jul;8(7):1878-84.

Barrett T *et al.*, NCBI GEO: archive for functional genomics data sets—10 years on, *Nucleic Acids Res*. 2011 January; 39(Database issue): D1005–D1010. Published online 2010 November 20. doi: 10.1093/nar/gkq1184

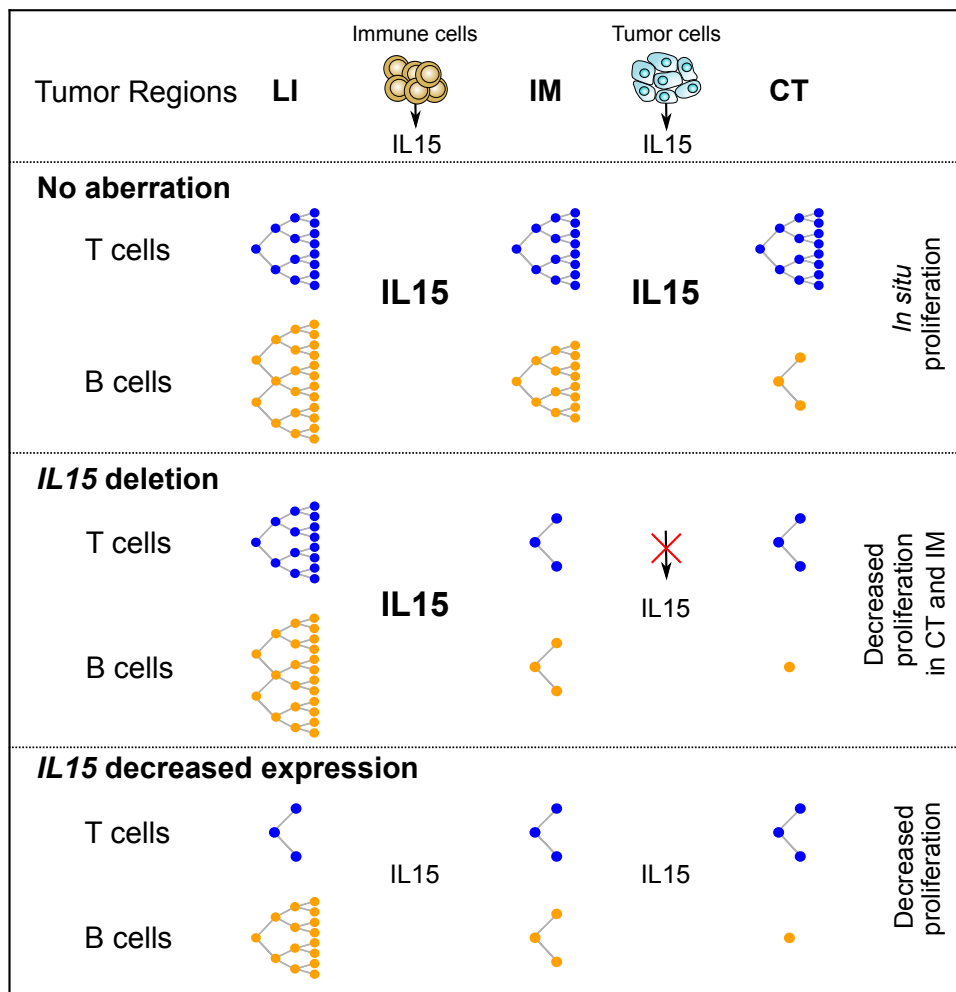
## **Supplementary Figure 2**

### **Schematic representation of IL15 impact on immune cell proliferation within tumors.**

IL15 is produced by both immune and tumor cells from different tumor regions: center of the tumor (CT), invasive margin (IM) and lymphoid islets (LI). The proliferation of T (blue) and B (orange) cells is shown in patients without aberrations (upper panel), patients with deletion (middle panel) and patients with decreased IL15 expression (lower panel).



Supplementary Figure 1



Supplementary Figure 2

| Family   | Type     | Symbol   | Chromosome | Strand    | Start     | Stop      | EntrezID  | RepresentativeID |
|----------|----------|----------|------------|-----------|-----------|-----------|-----------|------------------|
| IFN      | soluble  | IFNA1    | 9          | 1         | 21430440  | 21431315  | 3439      | NM_024013        |
|          | soluble  | IFNA17   | 9          | -1        | 21217242  | 21218221  | 3451      | M38289           |
|          | soluble  | IFNA2    | 9          | -1        | 21374254  | 21375396  | 3440      | M54886           |
|          | soluble  | IFNA5    | 9          | -1        | 21294686  | 21295255  | 3442      | NM_002169        |
|          | soluble  | IFNA6    | 9          | -1        | 21340317  | 21340886  | 3443      | NM_021002        |
|          | soluble  | IFNA8    | 9          | 1         | 21399133  | 21400174  | 3445      | NM_002170        |
|          | soluble  | IFNG     | 12         | -1        | 66834817  | 66839788  | 3458      | M29383           |
| IFNR     | receptor | IFNAR1   | 21         | 1         | 33619084  | 33653999  | 3454      | NM_000629        |
|          | receptor | IFNAR2   | 21         | 1         | 33524101  | 33558697  | 3455      | L41944           |
|          | receptor | IFNGR1   | 6          | -1        | 137560315 | 137582200 | 3459      | AF056979         |
|          | receptor | IFNGR2   | 21         | 1         | 33697072  | 33731696  | 3460      | NM_005534        |
| IL       | soluble  | CSF1     | 1          | 1         | 110254980 | 110273878 | 1435      | NM_000757        |
|          | soluble  | IL10     | 1          | -1        | 205007571 | 205012462 | 3586      | NM_000572        |
|          | soluble  | IL24     | 1          | 1         | 205137412 | 205144107 | 11009     | NM_006850        |
|          | soluble  | IL1A     | 2          | -1        | 113247963 | 113259442 | 3552      | M15329           |
|          | soluble  | IL1B     | 2          | -1        | 113303808 | 113310827 | 3553      | M15330           |
|          | soluble  | IL12A    | 3          | 1         | 161189323 | 161196500 | 3592      | NM_000882        |
|          | soluble  | IL8      | 4          | 1         | 74825139  | 74828297  | 3576      | AF043337         |
|          | soluble  | IL2      | 4          | -1        | 123592075 | 123597330 | 3558      | NM_000586        |
|          | soluble  | IL21     | 4          | -1        | 123753234 | 123761662 | 59067     | NM_021803        |
|          | soluble  | IL15     | 4          | 1         | 142777204 | 142874062 | 3600      | Y09908           |
|          | soluble  | IL3      | 5          | 1         | 131424246 | 131426795 | 3562      | NM_000588        |
|          | soluble  | CSF2     | 5          | 1         | 131437384 | 131439758 | 1437      | NM_000758        |
|          | soluble  | IL5      | 5          | -1        | 131905035 | 131907113 | 3567      | NM_000879        |
|          | soluble  | IL13     | 5          | 1         | 132021764 | 132024700 | 3596      | NM_002188        |
|          | soluble  | IL4      | 5          | 1         | 132037272 | 132046267 | 3565      | NM_000589        |
|          | soluble  | IL9      | 5          | -1        | 135255834 | 135259415 | 3578      | NM_000590        |
|          | soluble  | IL12B    | 5          | -1        | 158674369 | 158690059 | 3593      | NM_002187        |
|          | soluble  | IL17A    | 6          | 1         | 52159144  | 52163395  | 3605      | Z58820           |
|          | soluble  | IL6      | 7          | 1         | 22733345  | 22738141  | 3569      | NM_000600        |
|          | soluble  | IL7      | 8          | -1        | 79807560  | 79880313  | 3574      | NM_000880        |
| soluble  | IL18     | 11       | -1         | 111519186 | 111540050 | 3606      | NM_001562 |                  |
| soluble  | IL23A    | 12       | 1          | 55018930  | 55020461  | 51561     | NM_016584 |                  |
| soluble  | IL27     | 16       | -1         | 28418184  | 28425656  | 246778    | NM_145659 |                  |
| soluble  | CSF3     | 17       | 1          | 35425214  | 35427592  | 1440      | NM_000759 |                  |
| soluble  | IL29     | 19       | 1          | 44478805  | 44481152  | 282618    | NM_172140 |                  |
| ILR      | receptor | IL10RB   | 21         | 1         | 33560542  | 33591390  | 3588      | BC001903         |
|          | receptor | IL12RB1  | 19         | -1        | 18031371  | 18058697  | 3594      | NM_005535        |
|          | receptor | IL12RB2  | 1          | 1         | 67545635  | 67635171  | 3595      | NM_001559        |
|          | receptor | IL15RA   | 10         | -1        | 6034340   | 6060148   | 3601      | NM_002189        |
|          | receptor | IL17RA   | 22         | 1         | 15945858  | 15971405  | 23765     | NM_014339        |
|          | receptor | IL17RB   | 3          | 1         | 53855612  | 53874867  | 55540     | NM_018725        |
|          | receptor | IL1R1    | 2          | 1         | 102136834 | 102162766 | 3554      | AK026803         |
|          | receptor | IL21R    | 16         | 1         | 27321224  | 27369616  | 50615     | AF269133         |
|          | receptor | IL23R    | 1          | 1         | 67404757  | 67498250  | 149233    | NM_144701        |
|          | receptor | IL28RA   | 1          | -1        | 24353234  | 24386338  | 163702    | NM_170743        |
|          | receptor | IL2RA    | 10         | -1        | 6093512   | 6144278   | 3559      | K03122           |
|          | receptor | IL2RB    | 22         | -1        | 35851824  | 35875908  | 3560      | NM_000878        |
|          | receptor | IL31RA   | 5          | 1         | 55185070  | 55248705  | 133396    | NM_001242636     |
|          | receptor | IL4R     | 16         | 1         | 27232752  | 27283600  | 3566      | NM_000418        |
| receptor | IL7R     | 5        | 1          | 35892748  | 35912681  | 3575      | NM_002185 |                  |
| receptor | IL8RA    | 2        | -1         | 218735813 | 218739961 | 3577      | NM_000634 |                  |
| receptor | IL8RB    | 2        | 1          | 218698991 | 218710220 | 3579      | NM_001557 |                  |
| TGF      | soluble  | TGFB1    | 19         | -1        | 46528491  | 46551656  | 7040      | BC000125         |
|          | receptor | TGFBR1   | 9          | 1         | 100907233 | 100956295 | 7046      | NM_004612        |
|          | receptor | TGFBR2   | 3          | 1         | 30622998  | 30710638  | 7048      | D50683           |
| TNF      | soluble  | TNF      | 6          | 1         | 31651329  | 31654091  | 7124      | NM_000594        |
|          | soluble  | TNFRSF1A | 12         | -1        | 6308184   | 6321522   | 7132      | NM_001065        |
|          | soluble  | TNFRSF1B | 1          | 1         | 12149647  | 12191864  | 7133      | NM_001066        |

Table S1. Cytokines investigated in CRC: Families and the chromosomal location.

| NAME     | Amplifications |           |               |       | Deletions |           |               |       |
|----------|----------------|-----------|---------------|-------|-----------|-----------|---------------|-------|
|          | # Pts          | Frequency | MeanAberation | Score | # Pts     | Frequency | MeanAberation | Score |
| CSF1     | 1              | 0.92      | 0.40          | 0.37  | 15        | 13.76     | -0.43         | -5.85 |
| CSF2     | 6              | 5.50      | 0.28          | 1.51  | 11        | 10.09     | -0.41         | -4.11 |
| CSF3     | 13             | 11.93     | 0.39          | 4.66  | 8         | 7.34      | -0.44         | -3.20 |
| IFNA1    | 14             | 12.84     | 0.40          | 5.12  | 9         | 8.26      | -0.45         | -3.76 |
| IFNA17   | 14             | 12.84     | 0.41          | 5.25  | 9         | 8.26      | -0.45         | -3.76 |
| IFNA2    | 14             | 12.84     | 0.41          | 5.25  | 9         | 8.26      | -0.45         | -3.76 |
| IFNA5    | 14             | 12.84     | 0.41          | 5.25  | 9         | 8.26      | -0.45         | -3.76 |
| IFNA6    | 14             | 12.84     | 0.41          | 5.25  | 9         | 8.26      | -0.45         | -3.76 |
| IFNA8    | 14             | 12.84     | 0.41          | 5.25  | 9         | 8.26      | -0.45         | -3.76 |
| IFNAR1   | 6              | 5.50      | 0.35          | 1.91  | 12        | 11.01     | -0.37         | -4.12 |
| IFNAR2   | 5              | 4.59      | 0.35          | 1.60  | 12        | 11.01     | -0.37         | -4.12 |
| IFNG     | 14             | 12.84     | 0.38          | 4.90  | 2         | 1.83      | -0.38         | -0.70 |
| IFNGR1   | 8              | 7.34      | 0.32          | 2.35  | 6         | 5.50      | -0.39         | -2.13 |
| IFNGR2   | 6              | 5.50      | 0.35          | 1.91  | 12        | 11.01     | -0.37         | -4.12 |
| IL10     | 14             | 12.84     | 0.48          | 6.20  | 3         | 2.75      | -0.34         | -0.93 |
| IL10RB   | 6              | 5.50      | 0.35          | 1.91  | 12        | 11.01     | -0.37         | -4.12 |
| IL12A    | 6              | 5.50      | 0.30          | 1.65  | 4         | 3.67      | -0.37         | -1.34 |
| IL12B    | 7              | 6.42      | 0.31          | 2.00  | 5         | 4.59      | -0.36         | -1.64 |
| IL12RB1  | 23             | 21.10     | 0.44          | 9.18  | 8         | 7.34      | -0.45         | -3.27 |
| IL12RB2  | 1              | 0.92      | 0.40          | 0.37  | 17        | 15.60     | -0.44         | -6.88 |
| IL13     | 6              | 5.50      | 0.28          | 1.51  | 11        | 10.09     | -0.41         | -4.11 |
| IL15     | 4              | 3.67      | 0.38          | 1.39  | 18        | 16.51     | -0.49         | -8.03 |
| IL15RA   | 7              | 6.42      | 0.43          | 2.78  | 7         | 6.42      | -0.33         | -2.11 |
| IL17A    | 13             | 11.93     | 0.44          | 5.28  | 4         | 3.67      | -0.41         | -1.51 |
| IL17RA   | 4              | 3.67      | 0.27          | 1.01  | 18        | 16.51     | -0.38         | -6.29 |
| IL17RB   | 6              | 5.50      | 0.28          | 1.57  | 5         | 4.59      | -0.34         | -1.56 |
| IL18     | 9              | 8.26      | 0.34          | 2.80  | 6         | 5.50      | -0.41         | -2.24 |
| IL1A     | 13             | 11.93     | 0.37          | 4.43  | 2         | 1.83      | -0.30         | -0.55 |
| IL1B     | 13             | 11.93     | 0.37          | 4.43  | 2         | 1.83      | -0.30         | -0.55 |
| IL1R1    | 12             | 11.01     | 0.34          | 3.72  | 2         | 1.83      | -0.30         | -0.55 |
| IL2      | 3              | 2.75      | 0.34          | 0.94  | 20        | 18.35     | -0.46         | -8.53 |
| IL21     | 3              | 2.75      | 0.34          | 0.94  | 20        | 18.35     | -0.46         | -8.53 |
| IL21R    | 18             | 16.51     | 0.39          | 6.49  | 5         | 4.59      | -0.35         | -1.62 |
| IL23A    | 20             | 18.35     | 0.39          | 7.18  | 3         | 2.75      | -0.43         | -1.18 |
| IL23R    | 1              | 0.92      | 0.40          | 0.37  | 18        | 16.51     | -0.46         | -7.55 |
| IL24     | 14             | 12.84     | 0.48          | 6.20  | 2         | 1.83      | -0.30         | -0.54 |
| IL27     | 24             | 22.02     | 0.47          | 10.25 | 5         | 4.59      | -0.48         | -2.20 |
| IL28RA   | 4              | 3.67      | 0.40          | 1.46  | 25        | 22.94     | -0.40         | -9.22 |
| IL29     | 23             | 21.10     | 0.49          | 10.24 | 5         | 4.59      | -0.42         | -1.94 |
| IL2RA    | 7              | 6.42      | 0.43          | 2.78  | 7         | 6.42      | -0.33         | -2.11 |
| IL2RB    | 7              | 6.42      | 0.42          | 2.67  | 21        | 19.27     | -0.41         | -7.98 |
| IL3      | 6              | 5.50      | 0.28          | 1.51  | 11        | 10.09     | -0.41         | -4.11 |
| IL31RA   | 6              | 5.50      | 0.26          | 1.46  | 7         | 6.42      | -0.35         | -2.26 |
| IL4      | 6              | 5.50      | 0.28          | 1.51  | 11        | 10.09     | -0.41         | -4.11 |
| IL4R     | 18             | 16.51     | 0.39          | 6.49  | 5         | 4.59      | -0.35         | -1.62 |
| IL5      | 6              | 5.50      | 0.28          | 1.51  | 11        | 10.09     | -0.41         | -4.11 |
| IL6      | 44             | 40.37     | 0.46          | 18.41 | 0         | 0.00      | 0.00          | 0.00  |
| IL7      | 30             | 27.52     | 0.42          | 11.61 | 5         | 4.59      | -0.46         | -2.12 |
| IL7R     | 15             | 13.76     | 0.43          | 5.89  | 3         | 2.75      | -0.38         | -1.03 |
| IL8      | 3              | 2.75      | 0.30          | 0.81  | 18        | 16.51     | -0.48         | -7.95 |
| IL8RA    | 15             | 13.76     | 0.38          | 5.26  | 5         | 4.59      | -0.31         | -1.42 |
| IL8RB    | 15             | 13.76     | 0.38          | 5.26  | 5         | 4.59      | -0.31         | -1.42 |
| IL9      | 10             | 9.17      | 0.34          | 3.16  | 8         | 7.34      | -0.35         | -2.53 |
| TGFB1    | 21             | 19.27     | 0.41          | 7.89  | 5         | 4.59      | -0.38         | -1.76 |
| TGFBR1   | 9              | 8.26      | 0.42          | 3.46  | 6         | 5.50      | -0.37         | -2.05 |
| TGFBR2   | 7              | 6.42      | 0.29          | 1.87  | 5         | 4.59      | -0.34         | -1.56 |
| TNF      | 16             | 14.68     | 0.46          | 6.68  | 10        | 9.17      | -0.44         | -4.01 |
| TNFRSF1A | 25             | 22.94     | 0.46          | 10.60 | 5         | 4.59      | -0.36         | -1.66 |
| TNFRSF1B | 6              | 5.50      | 0.38          | 2.10  | 20        | 18.35     | -0.40         | -7.29 |

Table S2. Genomic alterations of cytokines in CRC.

| NAME     | Fisher Exact Test: Amp-vs-No (Contingency Table) |      |      |       |       | Fisher Exact Test: Del-vs-No (Contingency Table) |      |      |       |       |
|----------|--|------|------|-------|-------|--|------|------|-------|-------|
|          | PValue-Amp-vs-No                                 | M0No | M1No | M0Amp | M1Amp | PValue-Del-vs-No                                 | M0No | M1No | M0Del | M1Del |
| CSF1     | 1.000  | 70   | 23   | 1     | 0     | 1.000  | 70   | 23   | 12    | 3     |
| CSF2     | 1.000  | 71   | 21   | 5     | 1     | 0.455  | 71   | 21   | 7     | 4     |
| CSF3     | 0.182  | 65   | 23   | 12    | 1     | 1.000  | 65   | 23   | 6     | 2     |
| IFNA1    | 0.083  | 69   | 17   | 8     | 6     | 0.392  | 69   | 17   | 6     | 3     |
| IFNA17   | 0.083  | 69   | 17   | 8     | 6     | 0.392  | 69   | 17   | 6     | 3     |
| IFNA2    | 0.083  | 69   | 17   | 8     | 6     | 0.392  | 69   | 17   | 6     | 3     |
| IFNA5    | 0.083  | 69   | 17   | 8     | 6     | 0.392  | 69   | 17   | 6     | 3     |
| IFNA6    | 0.083  | 69   | 17   | 8     | 6     | 0.392  | 69   | 17   | 6     | 3     |
| IFNA8    | 0.083  | 69   | 17   | 8     | 6     | 0.392  | 69   | 17   | 6     | 3     |
| IFNAR1   | 0.330  | 68   | 23   | 6     | 0     | 1.000  | 68   | 23   | 9     | 3     |
| IFNAR2   | 0.335  | 69   | 23   | 5     | 0     | 1.000  | 69   | 23   | 9     | 3     |
| IFNG     | 0.184  | 70   | 23   | 13    | 1     | 0.067  | 70   | 23   | 0     | 2     |
| IFNGR1   | 1.000  | 74   | 21   | 6     | 2     | 0.144  | 74   | 21   | 3     | 3     |
| IFNGR2   | 0.330  | 68   | 23   | 6     | 0     | 1.000  | 68   | 23   | 9     | 3     |
| IL10     | 1.000  | 69   | 23   | 11    | 3     | 1.000  | 69   | 23   | 3     | 0     |
| IL10RB   | 0.330  | 68   | 23   | 6     | 0     | 1.000  | 68   | 23   | 9     | 3     |
| IL12A    | 0.131  | 78   | 21   | 3     | 3     | 0.215  | 78   | 21   | 2     | 2     |
| IL12B    | 1.000  | 75   | 22   | 6     | 1     | 0.093  | 75   | 22   | 2     | 3     |
| IL12RB1  | 0.421  | 57   | 21   | 19    | 4     | 0.674  | 57   | 21   | 7     | 1     |
| IL12RB2  | 1.000  | 68   | 23   | 1     | 0     | 0.758  | 68   | 23   | 14    | 3     |
| IL13     | 1.000  | 71   | 21   | 5     | 1     | 0.455  | 71   | 21   | 7     | 4     |
| IL15     | 0.157  | 72   | 15   | 2     | 2     | 0.005  | 72   | 15   | 9     | 9     |
| IL15RA   | 0.654  | 74   | 21   | 5     | 2     | 0.351  | 74   | 21   | 4     | 3     |
| IL17A    | 0.728  | 70   | 22   | 11    | 2     | 0.259  | 70   | 22   | 2     | 2     |
| IL17RA   | 0.572  | 67   | 20   | 4     | 0     | 0.376  | 67   | 20   | 12    | 6     |
| IL17RB   | 1.000  | 75   | 23   | 5     | 1     | 0.593  | 75   | 23   | 3     | 2     |
| IL18     | 0.095  | 76   | 18   | 5     | 4     | 0.020  | 76   | 18   | 2     | 4     |
| IL1A     | 1.000  | 72   | 22   | 10    | 3     | 0.424  | 72   | 22   | 1     | 1     |
| IL1B     | 1.000  | 72   | 22   | 10    | 3     | 0.424  | 72   | 22   | 1     | 1     |
| IL1R1    | 1.000  | 73   | 22   | 9     | 3     | 0.420  | 73   | 22   | 1     | 1     |
| IL2      | 0.475  | 70   | 16   | 2     | 1     | 0.019  | 70   | 16   | 11    | 9     |
| IL21     | 0.475  | 70   | 16   | 2     | 1     | 0.019  | 70   | 16   | 11    | 9     |
| IL21R    | 1.000  | 65   | 21   | 14    | 4     | 1.000  | 65   | 21   | 4     | 1     |
| IL23A    | 0.038  | 62   | 24   | 19    | 1     | 1.000  | 62   | 24   | 2     | 1     |
| IL23R    | 1.000  | 67   | 23   | 1     | 0     | 0.553  | 67   | 23   | 15    | 3     |
| IL24     | 1.000  | 70   | 23   | 11    | 3     | 1.000  | 70   | 23   | 2     | 0     |
| IL27     | 1.000  | 61   | 19   | 18    | 6     | 1.000  | 61   | 19   | 4     | 1     |
| IL28RA   | 0.568  | 59   | 21   | 4     | 0     | 0.605  | 59   | 21   | 20    | 5     |
| IL29     | 0.422  | 59   | 22   | 19    | 4     | 0.322  | 59   | 22   | 5     | 0     |
| IL2RA    | 0.654  | 74   | 21   | 5     | 2     | 0.351  | 74   | 21   | 4     | 3     |
| IL2RB    | 0.337  | 63   | 18   | 7     | 0     | 0.163  | 63   | 18   | 13    | 8     |
| IL3      | 1.000  | 71   | 21   | 5     | 1     | 0.455  | 71   | 21   | 7     | 4     |
| IL31RA   | 1.000  | 74   | 22   | 5     | 1     | 0.356  | 74   | 22   | 4     | 3     |
| IL4      | 1.000  | 71   | 21   | 5     | 1     | 0.455  | 71   | 21   | 7     | 4     |
| IL4R     | 1.000  | 65   | 21   | 14    | 4     | 1.000  | 65   | 21   | 4     | 1     |
| IL5      | 1.000  | 71   | 21   | 5     | 1     | 0.455  | 71   | 21   | 7     | 4     |
| IL6      | 0.502  | 51   | 14   | 32    | 12    | 1.000  | 51   | 14   | 0     | 0     |
| IL7      | 1.000  | 58   | 16   | 23    | 7     | 0.087  | 58   | 16   | 2     | 3     |
| IL7R     | 1.000  | 70   | 21   | 12    | 3     | 0.147  | 70   | 21   | 1     | 2     |
| IL8      | 0.466  | 72   | 16   | 2     | 1     | 0.012  | 72   | 16   | 9     | 9     |
| IL8RA    | 0.108  | 64   | 25   | 14    | 1     | 0.320  | 64   | 25   | 5     | 0     |
| IL8RB    | 0.108  | 64   | 25   | 14    | 1     | 0.320  | 64   | 25   | 5     | 0     |
| IL9      | 1.000  | 71   | 20   | 8     | 2     | 0.095  | 71   | 20   | 4     | 4     |
| TGFB1    | 0.582  | 61   | 22   | 17    | 4     | 0.325  | 61   | 22   | 5     | 0     |
| TGFBR1   | 1.000  | 72   | 22   | 7     | 2     | 0.628  | 72   | 22   | 4     | 2     |
| TGFBR2   | 0.661  | 75   | 22   | 5     | 2     | 0.336  | 75   | 22   | 3     | 2     |
| TNF      | 0.344  | 61   | 22   | 14    | 2     | 1.000  | 61   | 22   | 8     | 2     |
| TNFRSF1A | 0.055  | 57   | 22   | 23    | 2     | 0.621  | 57   | 22   | 3     | 2     |
| TNFRSF1B | 0.185  | 59   | 24   | 6     | 0     | 0.093  | 59   | 24   | 18    | 2     |

Table S3. Genomic alterations of cytokines in relation with metastasis of CRC patients.



| NAME     | # Amp | # Del | # No | TTest.pv.Amp.vs.No | TTest.pv.Del.vs.No | HR.Amp.vs.No | LogRank.pv.Amp.vs.No | HR.Del.vs.No | LogRank.pv.Del.vs.No |
|----------|-------|-------|------|--------------------|--------------------|--------------|----------------------|--------------|----------------------|
| CSF1     | 1     | 15    | 93   | NA                 | 0.763              | NA           | NA                   | 0.75         | 0.587                |
| CSF2     | 6     | 11    | 92   | 0.605              | 0.220              | 1.37         | 0.569                | 0.87         | 0.782                |
| CSF3     | 13    | 8     | 88   | 0.200              | 0.766              | 0.66         | 0.437                | 0.63         | 0.483                |
| IFNA1    | 14    | 9     | 86   | 0.032              | 0.949              | 1.35         | 0.537                | 1.68         | 0.304                |
| IFNA17   | 14    | 9     | 86   | 0.071              | 0.503              | 1.35         | 0.537                | 1.68         | 0.304                |
| IFNA2    | 14    | 9     | 86   | 0.033              | 0.523              | 1.35         | 0.537                | 1.68         | 0.304                |
| IFNA5    | 14    | 9     | 86   | 0.261              | 0.707              | 1.35         | 0.537                | 1.68         | 0.304                |
| IFNA6    | 14    | 9     | 86   | 0.031              | 0.727              | 1.35         | 0.537                | 1.68         | 0.304                |
| IFNA8    | 14    | 9     | 86   | 0.215              | 0.915              | 1.35         | 0.537                | 1.68         | 0.304                |
| IFNAR1   | 6     | 12    | 91   | 0.005              | 0.030              | 1.05         | 0.872                | 0.69         | 0.523                |
| IFNAR2   | 5     | 12    | 92   | 0.009              | 0.159              | 1.41         | 0.485                | 0.70         | 0.542                |
| IFNG     | 14    | 2     | 93   | 0.342              | 0.537              | 0.93         | 0.949                | 1.78         | 0.619                |
| IFNGR1   | 8     | 6     | 95   | 0.467              | 0.075              | 0.59         | 0.449                | 2.33         | 0.101                |
| IFNGR2   | 6     | 12    | 91   | 0.001              | 0.076              | 1.05         | 0.872                | 0.69         | 0.523                |
| IL10     | 14    | 3     | 92   | 0.257              | 0.615              | 1.56         | 0.211                | 0.00         | 0.312                |
| IL10RB   | 6     | 12    | 91   | 0.059              | 0.049              | 1.05         | 0.872                | 0.69         | 0.523                |
| IL12A    | 41    | 1     | 67   | 0.918              | NA                 | 1.07         | 0.818                | NA           | NA                   |
| IL12B    | 7     | 5     | 97   | 0.459              | 0.521              | 1.08         | 0.879                | 1.78         | 0.307                |
| IL12RB1  | 23    | 8     | 78   | 0.377              | 0.299              | 0.60         | 0.213                | 0.00         | 0.024                |
| IL12RB2  | 1     | 17    | 91   | NA                 | 0.472              | NA           | NA                   | 0.54         | 0.234                |
| IL13     | 6     | 11    | 92   | 0.772              | 0.823              | 1.37         | 0.569                | 0.87         | 0.782                |
| IL15     | 4     | 18    | 87   | 0.973              | 0.008              | 2.09         | 0.219                | 2.23         | 0.039                |
| IL15RA   | 7     | 7     | 95   | 0.117              | 0.271              | 1.27         | 0.656                | 0.88         | 0.820                |
| IL17A    | 13    | 4     | 92   | 0.620              | 0.723              | 0.85         | 0.779                | 1.49         | 0.574                |
| IL17RA   | 4     | 18    | 87   | 0.340              | 0.931              | 0.00         | 0.138                | 1.09         | 0.882                |
| IL17RB   | 6     | 5     | 98   | 0.405              | 0.501              | 0.38         | 0.303                | 1.67         | 0.527                |
| IL18     | 9     | 6     | 94   | 0.896              | 0.133              | 2.33         | 0.093                | 2.29         | 0.212                |
| IL1A     | 13    | 2     | 94   | 0.773              | 0.187              | 1.30         | 0.519                | 3.14         | 0.281                |
| IL1B     | 13    | 2     | 94   | 0.781              | 0.506              | 1.30         | 0.519                | 3.14         | 0.281                |
| IL1R1    | 12    | 2     | 95   | 0.504              | 0.180              | 1.36         | 0.452                | 3.18         | 0.276                |
| IL2      | 3     | 20    | 86   | 0.035              | 0.911              | 1.46         | 0.573                | 2.22         | 0.029                |
| IL21     | 3     | 20    | 86   | 0.038              | 0.317              | 1.46         | 0.573                | 2.22         | 0.029                |
| IL21R    | 18    | 5     | 86   | 0.846              | 0.386              | 1.36         | 0.372                | 0.49         | 0.494                |
| IL23A    | 20    | 3     | 86   | 0.338              | 0.619              | 0.73         | 0.519                | 0.00         | 0.231                |
| IL23R    | 1     | 18    | 90   | NA                 | 0.407              | NA           | NA                   | 0.50         | 0.171                |
| IL24     | 14    | 2     | 93   | 0.719              | 0.966              | 1.57         | 0.206                | 0.00         | 0.381                |
| IL27     | 24    | 5     | 80   | 0.681              | 0.564              | 1.25         | 0.506                | 0.49         | 0.491                |
| IL28RA   | 4     | 25    | 80   | 0.991              | 0.461              | 0.49         | 0.483                | 0.59         | 0.182                |
| IL29     | 23    | 5     | 81   | 0.994              | 0.215              | 0.62         | 0.261                | 0.00         | 0.090                |
| IL2RA    | 7     | 7     | 95   | 0.278              | 0.664              | 1.27         | 0.656                | 0.88         | 0.820                |
| IL2RB    | 7     | 21    | 81   | 0.926              | 0.930              | 0.00         | 0.052                | 1.01         | 0.920                |
| IL3      | 6     | 11    | 92   | 0.095              | 0.727              | 1.37         | 0.569                | 0.87         | 0.782                |
| IL31RA   | 6     | 7     | 96   | 0.296              | 0.738              | 1.39         | 0.550                | 1.04         | 0.929                |
| IL4      | 6     | 11    | 92   | 0.000              | 0.306              | 1.37         | 0.569                | 0.87         | 0.782                |
| IL4R     | 18    | 5     | 86   | 0.125              | 0.703              | 1.36         | 0.372                | 0.49         | 0.494                |
| IL5      | 6     | 11    | 92   | 0.725              | 0.154              | 1.37         | 0.569                | 0.87         | 0.782                |
| IL6      | 44    | 0     | 65   | 0.154              | NA                 | 1.46         | 0.200                | NA           | NA                   |
| IL7      | 30    | 5     | 74   | 0.185              | 0.334              | 0.93         | 0.850                | 1.09         | 0.903                |
| IL7R     | 15    | 3     | 91   | 0.904              | 0.247              | 1.14         | 0.711                | 1.34         | 0.805                |
| IL8      | 1     | 18    | 90   | NA                 | 0.868              | NA           | NA                   | 1.23         | 0.699                |
| IL8RA    | 15    | 5     | 89   | 0.671              | 0.730              | 0.66         | 0.423                | 0.00         | 0.146                |
| IL8RB    | 15    | 5     | 89   | 0.569              | 0.905              | 0.66         | 0.423                | 0.00         | 0.146                |
| IL9      | 10    | 8     | 91   | 0.423              | 0.003              | 1.25         | 0.636                | 1.38         | 0.543                |
| TGFB1    | 21    | 5     | 83   | 0.754              | 0.227              | 0.57         | 0.210                | 0.00         | 0.090                |
| TGFBR1   | 9     | 6     | 94   | 0.037              | 0.739              | 0.82         | 0.760                | 1.44         | 0.568                |
| TGFBR2   | 7     | 5     | 97   | 0.573              | 0.657              | 0.31         | 0.205                | 1.65         | 0.540                |
| TNF      | 16    | 10    | 83   | 0.488              | 0.729              | 0.80         | 0.657                | 0.44         | 0.241                |
| TNFRSF1A | 25    | 5     | 79   | 0.658              | 0.913              | 0.53         | 0.128                | 0.46         | 0.408                |
| TNFRSF1B | 6     | 20    | 83   | 0.380              | 0.245              | 0.32         | 0.239                | 0.38         | 0.055                |

Table S4. The impact of genomic alterations of cytokines on the gene expression and the CRC patient disease-free survival.

|                                    | Cohort1             | Cohort2             | Cohort3             | PValue |
|------------------------------------|---------------------|---------------------|---------------------|--------|
|                                    | No. of patients (%) | No. of patients (%) | No. of patients (%) |        |
| <b>UICC (TNM) stage</b>            |                     |                     |                     | 0.28   |
| I                                  | 19 (17.4)           | 20 (19)             | 11 (23.9)           |        |
| II                                 | 35 (32.1)           | 34 (32.4)           | 20 (43.5)           |        |
| III                                | 29 (26.6)           | 28 (26.7)           | 4 (8.7)             |        |
| IV                                 | 26 (23.9)           | 23 (21.9)           | 11 (23.9)           |        |
| <b>Tumor (T) stage</b>             |                     |                     |                     | 0.07   |
| pT1                                | 5 (4.6)             | 6 (5.7)             | 1 (2.2)             |        |
| pT2                                | 16 (14.7)           | 16 (15.2)           | 11 (23.9)           |        |
| pT3                                | 69 (63.3)           | 72 (68.6)           | 21 (45.7)           |        |
| pT4                                | 19 (17.4)           | 11 (10.5)           | 13 (28.3)           |        |
| <b>N Stage</b>                     |                     |                     |                     | 0.06   |
| N0                                 | 62 (57.4)           | 62 (59.6)           | 36 (78.3)           |        |
| N1                                 | 25 (23.1)           | 27 (26)             | 3 (6.5)             |        |
| N2                                 | 21 (19.4)           | 15 (14.4)           | 7 (15.2)            |        |
| <b>M Stage</b>                     |                     |                     |                     | 0.92   |
| M0                                 | 83 (76.1)           | 82 (78.1)           | 35 (76.1)           |        |
| M1                                 | 26 (23.9)           | 23 (21.9)           | 11 (23.9)           |        |
| <b>Age (yrs)</b>                   |                     |                     |                     | 0.62   |
| <65                                | 29 (26.6)           | 28 (26.7)           | 11 (23.9)           |        |
| 65-75                              | 26 (23.9)           | 25 (23.8)           | 13 (28.3)           |        |
| 75-85                              | 36 (33)             | 36 (34.3)           | 10 (21.7)           |        |
| > 85                               | 18 (16.5)           | 16 (15.2)           | 12 (26.1)           |        |
| <b>Gender</b>                      |                     |                     |                     | 0.05   |
| Male                               | 60 (55)             | 57 (54.3)           | 16 (34.8)           |        |
| Female                             | 49 (45)             | 48 (45.7)           | 30 (65.2)           |        |
| <b>Tumor Location</b>              |                     |                     |                     | 0.38   |
| Right colon                        | 32 (29.4)           | 37 (35.2)           | 15 (32.6)           |        |
| Left colon                         | 14 (12.8)           | 17 (16.2)           | 4 (8.7)             |        |
| Transverse colon                   | 10 (9.2)            | 8 (7.6)             | 3 (6.5)             |        |
| Sigmoid colon                      | 34 (31.2)           | 33 (31.4)           | 12 (26.1)           |        |
| Rectum                             | 19 (17.4)           | 10 (9.5)            | 12 (26.1)           |        |
| <b>Number of total lymph nodes</b> |                     |                     |                     | 0.91   |
| <8                                 | 35 (32.1)           | 34 (32.4)           | 13 (28.3)           |        |
| >=8                                | 74 (67.9)           | 71 (67.6)           | 33 (71.7)           |        |
| <b>Histological grade</b>          |                     |                     |                     | 0.18   |
| Well Differentiated                | 69 (63.3)           | 71 (67.6)           | 33 (71.7)           |        |
| Moderately Differentiated          | 39 (35.8)           | 31 (29.5)           | 10 (21.7)           |        |
| Poorly Differentiated              | 1 (0.9)             | 3 (2.9)             | 3 (6.5)             |        |
| <b>Occlusion</b>                   |                     |                     |                     | 0.53   |
| No                                 | 95 (87.2)           | 90 (85.7)           | 37 (80.4)           |        |
| Yes                                | 14 (12.8)           | 15 (14.3)           | 9 (19.6)            |        |
| <b>Perforation</b>                 |                     |                     |                     | 0.40   |
| No                                 | 107 (98.2)          | 104 (99)            | 44 (95.7)           |        |
| Yes                                | 2 (1.8)             | 1 (1)               | 2 (4.3)             |        |
| <b>Postoperative Treatment</b>     |                     |                     |                     | 0.14   |
| NON                                | 71 (65.1)           | 65 (61.9)           | 36 (78.3)           |        |
| CHIMIO                             | 38 (34.9)           | 40 (38.1)           | 10 (21.7)           |        |
| <b>Velipi</b>                      |                     |                     |                     | 0.66   |
| No                                 | 69 (65.1)           | 73 (70.9)           | 32 (69.6)           |        |
| Yes                                | 37 (34.9)           | 30 (29.1)           | 14 (30.4)           |        |
| <b>Relapse</b>                     |                     |                     |                     | 0.68   |
| NO                                 | 65 (59.6)           | 65 (61.9)           | 31 (67.4)           |        |
| YES                                | 44 (40.4)           | 40 (38.1)           | 15 (32.6)           |        |
| <b>Patient died</b>                |                     |                     |                     | 0.56   |
| NO                                 | 43 (39.4)           | 49 (46.7)           | 20 (43.5)           |        |
| YES                                | 66 (60.6)           | 56 (53.3)           | 26 (56.5)           |        |

Table S5. Clinical characteristics of the cohorts investigated.