Calcitonin receptor-like (CALCRL) is a marker of stemness and an independent predictor of outcome in pediatric AML

Linus Angenendt1, Marius Wöste2, Jan-Henrik Mikesch1, Maria Francisca Arteaga1, Adrian Angenendt3, Sarah Sandmann2, Wolfgang E. Berdel1, Georg Lenz1, Martin Dugas2, Soheil Meshinchi4, Christoph Schliemann1*, Claudia Rössig5*

1Department of Medicine A, University Hospital Münster, Münster, Germany;
2Institute of Medical Informatics, University of Münster, Münster, Germany;
3Department of Biophysics, Faculty of Medicine, Centre for Integrative Physiology and Molecular Medicine (CIPMM), Saarland University, Homburg, Germany;
4Clinical Research Division, Fred Hutchinson Cancer Research Center, Seattle, Washington, USA;
5Department of Pediatric Hematology and Oncology, University Children’s Hospital Münster, Münster, Germany.
*contributed equally

Corresponding author: Linus Angenendt, M.D., Department of Medicine A, University Hospital Münster, Albert-Schweitzer-Campus 1, 48149 Münster, Germany; Phone: +49 251 83 44846; Fax: +49 251 83 47588; Email: linus.angenendt@ukmuenster.de.
### Supplementary Table 1. List of the 200 differentially expressed genes with the lowest adjusted p values ordered by log fold change in \textit{CALCRL}^{high} compared to \textit{CALCRL}^{low} expressers.

| Gene name     | Probe set     | Log2 fold change | P value |
|---------------|---------------|------------------|---------|
| TNRFSF18      | ENSG00000186891 | 2.075            | 1.61E-17 |
| MSR1          | ENSG0000038945  | 2.026            | 9.13E-08 |
| CDCP1         | ENSG00000163814 | 1.940            | 1.01E-12 |
| MACC1         | ENSG00000183742 | 1.741            | 3.55E-09 |
| CXCL2         | ENSG0000081041  | 1.737            | 1.22E-09 |
| STAT4         | ENSG0000138378  | 1.551            | 1.35E-10 |
| SH3TC2        | ENSG0000169247  | 1.548            | 4.00E-08 |
| TMEZ204       | ENSG0000136134  | 1.475            | 1.73E-08 |
| ADAM28        | ENSG0000042980  | 1.276            | 2.56E-11 |
| CLIP4         | ENSG00000115295 | 1.142            | 3.97E-08 |
| ATP13A3       | ENSG00000133657 | 0.980            | 6.20E-08 |
| LPIN1         | ENSG00000134324 | 0.720            | 2.66E-09 |
| TADA3         | ENSG00000171148 | -0.686           | 9.64E-09 |
| GTF3C5        | ENSG00000148308 | -0.695           | 3.79E-09 |
| TESMIN        | ENSG00000012749 | -0.732           | 3.26E-08 |
| STXB2         | ENSG0000076944  | -0.780           | 1.56E-09 |
| CRAADD        | ENSG00000169372 | -0.794           | 6.89E-08 |
| SLC25A1       | ENSG00000100075 | -0.923           | 3.41E-10 |
| ACO095506.1   | ENSG00000224152 | -0.961           | 1.02E-07 |
| SFMBT1        | ENSG00000163935 | -0.990           | 6.89E-08 |
| HYAL3         | ENSG00000186792 | -1.039           | 3.04E-09 |
| BARAM2        | ENSG00000189019 | -1.243           | 5.40E-10 |
| AC112484.3    | ENSG00000261159 | -1.310           | 1.22E-09 |
| EFEMP2        | ENSG00000172638 | -1.310           | 7.98E-09 |
| LINC02610     | ENSG000000186235 | -1.330          | 3.71E-08 |
| AC1316455.1   | ENSG00000256546 | -1.335           | 3.13E-08 |
| AL162231.2    | ENSG00000230074 | -1.359           | 5.28E-09 |
| SPINT1        | ENSG00000166145 | -1.413           | 4.37E-08 |
| PRR74         | ENSG000000224940 | -1.448          | 5.98E-08 |
| LINC02447     | ENSG00000245468 | -1.475           | 3.00E-08 |
| PLD3          | ENSG00000105223 | -1.513           | 1.56E-09 |
| KAZN          | ENSG00000189337 | -1.531           | 1.46E-08 |
| LRP3          | ENSG00000130881 | -1.545           | 8.38E-09 |
| PIN1YP        | ENSG00000234465 | -1.563           | 1.45E-09 |
| RPP25         | ENSG00000178718 | -1.600           | 3.96E-08 |
| CDK20         | ENSG00000156345 | -1.627           | 9.49E-09 |
| BGNMT4        | ENSG00000156966 | -1.640           | 1.46E-08 |
| AC1312106.1   | ENSG00000255836 | -1.646           | 6.95E-09 |
| TERT          | ENSG00000164362 | -1.693           | 9.64E-09 |
| PODXL2        | ENSG00000114631 | -1.694           | 2.99E-12 |
| MTIF          | ENSG00000198417 | -1.699           | 5.94E-09 |
| MACROD2       | ENSG00000172264 | -1.748           | 9.64E-09 |
| ADC9         | ENSG00000162104 | -1.772           | 1.56E-09 |
| SERINC2       | ENSG00000168528 | -1.773           | 1.06E-09 |
| COL14A1       | ENSG00000187955 | -1.809           | 4.49E-08 |
| CD70          | ENSG00000125726 | -1.853           | 6.98E-09 |
| ITGB4         | ENSG00000132470 | -1.870           | 2.19E-10 |
| GNA14         | ENSG00000156049 | -1.874           | 7.07E-08 |
| BCL2L10       | ENSG00000137875 | -1.879           | 6.87E-08 |
| C1orf98       | ENSG00000262874 | -1.922           | 1.40E-09 |
| GTF2IP7       | ENSG00000227038 | -1.972           | 7.80E-09 |
| AGRP          | ENSG00000159723 | -1.993           | 1.01E-10 |
| CLEC4G        | ENSG00000182566 | -1.998           | 3.29E-08 |
| GPBRN1        | ENSG00000162958 | -2.004           | 8.19E-10 |
| RCOO2         | ENSG00000167771 | -2.009           | 2.62E-10 |
| KCNK12        | ENSG00000184261 | -2.036           | 7.82E-13 |
| ALPK3         | ENSG00000136383 | -2.043           | 1.01E-10 |
**CALCRL in childhood AML**

| Gene      | ENSG00000109472 | -2.098 | 2.35E-09 |
|-----------|-----------------|--------|---------|
| DNAJC5B   | ENSG00000147570 | -2.107 | 3.82E-08 |
| GATM      | ENSG00000171766 | -2.111 | 7.13E-14 |
| TEAD2     | ENSG00000074219 | -2.122 | 1.42E-08 |
| PDCD6IPP2 | ENSG00000261377 | -2.125 | 5.28E-09 |
| NFE4      | ENSG00000230257 | -2.160 | 4.61E-11 |
| RSPO1     | ENSG00000169218 | -2.177 | 6.48E-09 |
| TUBB4A    | ENSG00000104833 | -2.183 | 1.56E-09 |
| ASS1      | ENSG00000137070 | -2.197 | 1.03E-08 |
| RAB11FIP5 | ENSG00000135631 | -2.252 | 1.93E-11 |
| CD163L1   | ENSG00000177765 | -2.271 | 1.30E-13 |
| GUICY1B2  | ENSG00000123201 | -2.286 | 5.94E-09 |
| AL031710.1| ENSG00000261399 | -2.308 | 5.55E-09 |
| CACNA2D2  | ENSG00000007402 | -2.352 | 2.56E-13 |
| ROB2      | ENSG00000169071 | -2.372 | 1.92E-10 |
| KLGP2     | ENSG00000188883 | -2.383 | 1.01E-10 |
| PTH1R     | ENSG00000160801 | -2.399 | 1.27E-08 |
| TKT1      | ENSG00000007350 | -2.410 | 4.60E-11 |
| CPT1C     | ENSG00000169169 | -2.414 | 6.30E-10 |
| NEO1      | ENSG00000067141 | -2.416 | 5.88E-11 |
| GREB1     | ENSG00000196208 | -2.440 | 1.81E-08 |
| SHE       | ENSG00000169291 | -2.442 | 1.57E-10 |
| FEZ1      | ENSG00000149557 | -2.455 | 1.13E-11 |
| ANKRD65   | ENSG00000235098 | -2.461 | 1.05E-08 |
| GP4M6B    | ENSG00000046653 | -2.468 | 1.82E-11 |
| CYB5R2    | ENSG00000166394 | -2.483 | 7.72E-09 |
| TRH       | ENSG00000170893 | -2.503 | 5.94E-09 |
| GAS1      | ENSG00000180447 | -2.505 | 5.28E-09 |
| AL713998.1| ENSG00000227706 | -2.516 | 8.37E-08 |
| CRABP1    | ENSG00000166426 | -2.523 | 1.34E-08 |
| USP2      | ENSG00000036672 | -2.535 | 9.41E-16 |
| AC021683.2| ENSG00000267506 | -2.602 | 6.42E-09 |
| DPY19L2P1 | ENSG00000189212 | -2.602 | 1.06E-09 |
| PXDN      | ENSG00000130508 | -2.603 | 9.97E-09 |
| PLP1      | ENSG00000160539 | -2.622 | 3.34E-12 |
| FBLN1     | ENSG00000077942 | -2.626 | 1.56E-09 |
| GALNTL6   | ENSG00000174473 | -2.633 | 1.18E-09 |
| GRIN2D    | ENSG00000105464 | -2.651 | 4.09E-19 |
| SLCTA10   | ENSG00000130876 | -2.656 | 2.12E-11 |
| FBLN5     | ENSG00000140092 | -2.658 | 4.44E-13 |
| INPP5J    | ENSG00000185133 | -2.680 | 4.75E-12 |
| STXBP6    | ENSG00000168952 | -2.699 | 2.92E-08 |
| SLC29A4   | ENSG00000164638 | -2.706 | 5.00E-21 |
| IL5RA     | ENSG00000091181 | -2.720 | 4.13E-15 |
| NCAM1     | ENSG00000149294 | -2.728 | 7.43E-10 |
| COL6A6    | ENSG00000206384 | -2.731 | 1.45E-09 |
| MYO6      | ENSG00000196586 | -2.739 | 6.91E-12 |
| APOC4-APOC2| ENSG00000224916 | -2.749 | 1.13E-15 |
| APOC2     | ENSG00000234906 | -2.752 | 1.10E-15 |
| GABRB1    | ENSG00000146276 | -2.789 | 3.55E-08 |
| C2orf66   | ENSG00000187944 | -2.835 | 1.20E-08 |
| SPAG6     | ENSG00000077327 | -2.836 | 7.55E-15 |
| EVC2      | ENSG00000173040 | -2.846 | 1.27E-08 |
| PKP2      | ENSG00000057294 | -2.848 | 1.22E-08 |
| TFF3      | ENSG00000160180 | -2.861 | 2.50E-10 |
| LAMC3     | ENSG00000050555 | -2.904 | 2.36E-18 |
| MEIOB     | ENSG00000162039 | -2.932 | 1.66E-09 |
| AC106865.1| ENSG00000250771 | -2.935 | 1.46E-09 |
| DLK1      | ENSG00000185559 | -2.952 | 5.86E-08 |
| LIN00689  | ENSG00000231419 | -2.954 | 8.61E-08 |
| LIN01257  | ENSG00000204603 | -2.989 | 1.13E-11 |
| SOBP      | ENSG00000112320 | -2.996 | 1.05E-17 |
| CPE       | ENSG00000109472 | -2.996 | 2.86E-09 |
### CALCR in childhood AML

| Gene   | ENSG ID | Log2 Fold Change | p-value |
|--------|---------|------------------|---------|
| ZNF503-AS1 | ENSG00000226051 | -3.024 | 1.83E-09 |
| SULT4A1   | ENSG00000130540 | -3.032 | 7.76E-08 |
| ADGRL2    | ENSG00000117114 | -3.044 | 7.96E-08 |
| C3orf14   | ENSG00000114405 | -3.044 | 3.43E-09 |
| AC024475.2 | ENSG00000255314 | -3.055 | 5.18E-08 |
| GLIS3     | ENSG00000107249 | -3.085 | 1.52E-14 |
| DDI4L     | ENSG00000145358 | -3.106 | 1.34E-08 |
| TGM5      | ENSG00000112276 | -3.115 | 6.03E-16 |
| BVES      | ENSG000001122276| -3.122 | 3.73E-08 |
| POU4F1    | ENSG00000152192 | -3.123 | 1.32E-08 |
| MTCO3P12  | ENSG00000198744 | -3.124 | 2.42E-22 |
| PARD3B    | ENSG00000116117 | -3.146 | 3.04E-09 |
| PRL       | ENSG00000172179 | -3.157 | 4.33E-08 |
| LINC01529 | ENSG00000225872 | -3.172 | 9.41E-11 |
| FIBCD1    | ENSG00000130720 | -3.185 | 2.15E-13 |
| TDRD10    | ENSG00000163239 | -3.241 | 3.01E-15 |
| DNAH2     | ENSG00000183914 | -3.265 | 1.37E-12 |
| DNAH8     | ENSG00000124721 | -3.272 | 1.57E-10 |
| LINC01731 | ENSG00000234283 | -3.285 | 5.11E-09 |
| GPC3      | ENSG00000147257 | -3.309 | 4.41E-10 |
| CLEC2L    | ENSG00000236279 | -3.340 | 7.28E-09 |
| FRAS1     | ENSG00000138759 | -3.353 | 1.33E-08 |
| WIPF3     | ENSG00000122574 | -3.433 | 7.49E-16 |
| CTNN43    | ENSG00000183230 | -3.459 | 3.57E-09 |
| EVC       | ENSG00000072840 | -3.464 | 2.59E-15 |
| RGS22     | ENSG00000132554 | -3.497 | 9.83E-10 |
| AC025569.1 | ENSG00000258168 | -3.586 | 1.16E-10 |
| CLSTN2    | ENSG00000158258 | -3.602 | 5.30E-13 |
| IL22RA2   | ENSG00000164485 | -3.615 | 7.91E-08 |
| LINC00477 | ENSG00000197503 | -3.625 | 9.70E-08 |
| PPP1R27   | ENSG00000182676 | -3.642 | 1.67E-22 |
| AC065829.2 | ENSG00000262539 | -3.657 | 3.55E-11 |
| HSPB6     | ENSG0000004777  | -3.697 | 1.42E-27 |
| AC050577.4 | ENSG00000230882 | -3.702 | 1.92E-17 |
| ALA50311.1 | ENSG00000236154 | -3.749 | 8.18E-15 |
| VAT1L     | ENSG00000171724 | -3.772 | 9.01E-13 |
| AC046168.2 | ENSG00000259420 | -3.827 | 1.93E-08 |
| MYO18B    | ENSG00000133454 | -3.858 | 2.94E-15 |
| PCLO      | ENSG00000186472 | -3.886 | 3.57E-09 |
| FOXL1     | ENSG00000176678 | -4.014 | 8.32E-13 |
| HSSST4    | ENSG00000182601 | -4.019 | 8.08E-10 |
| PRAME     | ENSG00000185686 | -4.074 | 1.67E-22 |
| NEUROG3   | ENSG00000122859 | -4.136 | 6.99E-12 |
| AP000439.2 | ENSG00000255980 | -4.153 | 6.51E-08 |
| DYNC11I   | ENSG00000158560 | -4.227 | 1.31E-11 |
| ROBO1     | ENSG00000169855 | -4.228 | 2.68E-19 |
| DLL3      | ENSG00000090932 | -4.248 | 2.52E-30 |
| ADAM23    | ENSG00000114948 | -4.310 | 3.53E-18 |
| FAM3B     | ENSG00000183844 | -4.312 | 1.83E-11 |
| LINC02506 | ENSG00000251129 | -4.346 | 1.37E-08 |
| PCDH10    | ENSG00000138650 | -4.416 | 3.10E-11 |
| KLK13     | ENSG00000167759 | -4.436 | 2.10E-08 |
| CADM1     | ENSG00000182985 | -4.450 | 1.23E-24 |
| SIX1      | ENSG00000138083 | -4.464 | 6.13E-13 |
| MTND1P23  | ENSG00000225972 | -4.516 | 1.23E-36 |
| MSX2      | ENSG00000120149 | -4.521 | 1.18E-09 |
| MAB2I14   | ENSG00000172478 | -4.538 | 4.76E-08 |
| LAMP5     | ENSG00000125869 | -4.608 | 1.21E-16 |
| WSCD1     | ENSG00000179314 | -4.613 | 9.74E-15 |
| CCD1C14NL | ENSG00000205212 | -4.641 | 3.37E-09 |
| C3orf58   | ENSG00000186493 | -4.734 | 9.91E-08 |
| LINC02600 | ENSG00000230986 | -4.973 | 5.54E-15 |
| CLEC2A    | ENSG00000188393 | -4.999 | 1.53E-11 |
CALCRL in childhood AML

| Gene       | Ensembl   | -Log10 P  | E-Value |
|------------|-----------|-----------|---------|
| KCNN2      | ENSG00000080709 | -5.015    | 2.68E-12 |
| TRPM4      | ENSG00000130529  | -5.132    | 1.39E-17 |
| KIAA1210   | ENSG00000250423  | -5.185    | 2.72E-09 |
| UNCS5C     | ENSG00000182168  | -5.238    | 3.33E-16 |
| KCNE5      | ENSG00000176076  | -5.255    | 3.36E-18 |
| HMX3       | ENSG00000188620  | -5.261    | 2.42E-18 |
| XAGIE1B    | ENSG00000204382  | -5.360    | 8.34E-08 |
| ABHD17AP6  | ENSG00000226981  | -5.371    | 7.46E-25 |
| LINCO1833  | ENSG00000259439  | -5.556    | 1.13E-11 |
| IGSF1      | ENSG00000147255  | -5.680    | 5.49E-15 |
| IRX6       | ENSG00000159387  | -5.698    | 2.10E-08 |
| HRC        | ENSG00000130528  | -5.703    | 4.09E-19 |
| PLAAT1     | ENSG00000127252  | -5.940    | 5.03E-11 |
| PENK       | ENSG00000181195  | -6.384    | 3.95E-19 |
| CNTN4      | ENSG00000144619  | -6.546    | 1.72E-32 |
| SOX11      | ENSG00000176887  | -6.579    | 3.41E-10 |
| AF181450.1 | ENSG00000253576  | -9.264    | 1.01E-11 |
**Supplementary Table 2. Gene expression signatures significantly enriched for genes of the CALCRL high expression profile in gene set enrichment analysis.**

| Signature name | ES  | NES  | NOM P          |
|----------------|-----|------|----------------|
| HOEBEKE_LYMPHOID_STEM_CELL_UP | 0.730 | 1.913 | <0.001         |
| EPPERT_HSC_R          | 0.758 | 1.855 | <0.001         |
| BARRIER_CANCER_RELAPSE_NORMAL_SAMPLE_UP | 0.737 | 1.817 | 0.001          |
| EPPERT_LSC_R          | 0.743 | 1.806 | 0.002          |
| VALK_AML_CLUSTER_2    | 0.947 | 1.755 | <0.001         |
| EPPERT_CE_HSC_LSC     | 0.854 | 1.749 | <0.001         |
| GRAHAM_CML_DIVIDING_VS_NORMAL_QUIESCENT_DN| 0.748 | 1.710 | <0.001         |
| ZHENG_FOXP3_TARGETS_IN_THYMUS_UP | 0.669 | 1.709 | 0.006          |
| GEISS_RESPONSE_TO_INDEXRNA_UP    | 0.707 | 1.702 | 0.003          |
| MARCINIAK_ER_STRESS_RESPONSE_VIA_CHOP | 0.643 | 1.700 | 0.002          |
| PID_FAS_PATHWAY        | 0.622 | 1.695 | 0.005          |
| GRAHAM_NORMAL_QUIESCENT_VS_NORMAL_DIVIDING_UP | 0.783 | 1.692 | 0.001          |
| GARGALOVIC_RESPONSE_TO_OXIDIZED_PHOSPHOLIPIDS_TURQUOISE_UP | 0.701 | 1.689 | 0.003          |
| LEE_INTRATHYMIC_T_PROGENITOR | 0.809 | 1.683 | 0.001          |
| TAKEDA_TARGETS_OF_NUP98_HOX9_FUSION_3D_UP | 0.720 | 1.675 | 0.001          |
| CHANDRAN_METASTASIS_TOP50_UP | 0.523 | 1.670 | 0.010          |
| PARK_HSC_MARKERS       | 0.566 | 1.669 | 0.004          |
| PID_IL1_PATHWAY        | 0.692 | 1.660 | 0.008          |
| MULLIGHAN_NPM1_MUTATED_SIGNATURE_1_UP | 0.612 | 1.658 | 0.003          |
| CHEN_PDGF_TARGETS      | 0.727 | 1.653 | 0.006          |
| VALK_AML_CLUSTER_3     | 0.818 | 1.650 | <0.001         |
| TIEN_INTESTINE_PROBIOTICS_2HR_DN | 0.591 | 1.647 | 0.008          |
| WATANABE_ULCERATIVE_COLITIS_WITH_CANCER_DN | 0.850 | 1.645 | 0.002          |
| REACTOME_CTLA4_INHIBITORY_SIGNALING | 0.727 | 1.644 | 0.008          |
| WORSCHECH_TUMOR_REJECTION_UP | 0.724 | 1.638 | 0.004          |
| FIGUEROA_AML_METHYLATION_CLUSTER_4_DN | 0.788 | 1.637 | 0.004          |
| MULLIGHAN_NPM1_SIGNATURE_3_UP | 0.584 | 1.633 | 0.007          |
| ZHENG_BOUND_BY_FOXP3   | 0.594 | 1.633 | 0.007          |
| VALK_AML_WITHFLT3_ITD  | 0.867 | 1.632 | <0.001         |
| SCHAEFFER_PROSTATE_DEVELOPMENT_AND_CANCER_BOX4_DN | 0.624 | 1.626 | 0.015          |
| KYNG_RESPONSE_TO_H2O2_VIA_ERCC6_UP | 0.584 | 1.625 | 0.007          |
| REACTOME_BETA_DEFENSINS | 0.614 | 1.621 | 0.042          |
| GENTLES_LEUKEMIC_STEM_CELL_UP | 0.791 | 1.621 | 0.005          |
| GRAHAM_CML_QUIESCENT_VS_NORMAL_QUIESCENT_DN | 0.781 | 1.618 | 0.006          |
| SESTO_RESPONSE_TO_UV_C2 | 0.636 | 1.612 | 0.009          |
| WP_ENDOTHELIN_PATHWAYS | 0.659 | 1.612 | 0.005          |
| GARGALOVIC_RESPONSE_TO_OXIDIZED_PHOSPHOLIPIDS_BLK_UP | 0.686 | 1.610 | 0.009          |
| PARK_HSC_VS_Multipotent_PROGENITORS_UP | 0.601 | 1.609 | 0.018          |
| PID_EPHNRN_REV_PATHWAY | 0.714 | 1.609 | 0.006          |
| WP_HEMATOPOIETIC_STEM_CELL_GENE_REGULATION_BY_GABP_ALPHABETA_ | 0.620 | 1.608 | 0.021          |
| WANG_RESPONSE_TO_ANDROGEN_UP | 0.606 | 1.607 | 0.013          |
| BROWNE_HCMV_INFECTION_6HR_DN | 0.558 | 1.604 | 0.003          |
| TAKEDA_TARGETS_OF_NUP98_HOX9_FUSION_8D_UP | 0.697 | 1.592 | 0.003          |
| DING_LUNG_CANCER_EXPRESSION_BY_COPY_NUMBER | 0.583 | 1.588 | 0.032          |
| SENSEE_HDAC2_TARGETS_UP | 0.604 | 1.586 | 0.013          |
| BIOCARTA_TNFR2_PATHWAY | 0.713 | 1.586 | 0.024          |
| GALE_APL_WITHFLT3_MUTATED_UP | 0.553 | 1.585 | 0.024          |
| REACTOME_GRB2_SOS_PROVIDES_LINKAGE_TO_MAPK_SIGNALING_FOR_INTEGRINS | 0.787 | 1.580 | 0.010          |
| TAKEDA_TARGETS_OF_NUP98_HOX9_FUSION_6HR_UP | 0.702 | 1.580 | 0.004          |
| BIOCARTA_NTH1_PATHWAY | 0.707 | 1.579 | 0.021          |
| DEURIG_T_CELL_PROLYMPHOCYTIC_LEUKEMIA_DN | 0.616 | 1.578 | 0.021          |
| REACTOME_NOD1_2_SIGNALING_PATHWAY | 0.567 | 1.575 | 0.024          |
| ZHENG_FOXP3_TARGETS_UP | 0.764 | 1.573 | 0.013          |
| WANG_IMMORTALIZED_BY_HOX9_AND_MEIS1_DN | 0.727 | 1.572 | 0.008          |
| REACTOME_PI3K_CASCADE_FGFR2 | 0.670 | 1.572 | 0.013          |
| DAZARD_RESPONSE_TO_UV_NHEK_DN | 0.582 | 1.571 | 0.021          |
| DE_Y11_TARGETS_DN | 0.643 | 1.571 | 0.024          |
| IKEDA_MIR1_TARGETS_UP | 0.641 | 1.568 | 0.024          |
| BYSTROEM_CORRELATED_WITH_IL5_DN | 0.568 | 1.565 | 0.037          |
**CALCR** in childhood AML

| Pathway Description                                                                 | Beta | Log2 Fold Change | P-Value  |
|------------------------------------------------------------------------------------|------|------------------|----------|
| Reactome Regulation of Runx1 Expression and Activity                              | 0.639| 1.563            | 0.033    |
| Mcbryan Pubertal Breast 6_7WK_Up                                                  | 0.528| 1.562            | 0.011    |
| Beier Glioma Stem Cell Up                                                         | 0.628| 1.561            | 0.005    |
| Pid NFAT Tpathway                                                                 | 0.715| 1.561            | 0.020    |
| Takeda Targets of Nup98_Hoxa9_Fusion 6HR_Dn                                       | 0.712| 1.560            | 0.013    |
| Brownie Hcmv Infection 12HR_Up                                                    | 0.558| 1.560            | 0.010    |
| Sotirioou Breast Cancer Grade 1 VS 3_Dn                                           | 0.578| 1.558            | 0.011    |
| Theilgaard Neutrophil At Skin Wound Up                                           | 0.673| 1.558            | 0.031    |
| Pid Nfkappaab Atypical Pathway                                                    | 0.670| 1.557            | 0.029    |
| Bosco Interferon Induced Antiviral Module                                         | 0.687| 1.557            | 0.021    |
| Marson Foxp1 Targets_Dn                                                           | 0.614| 1.556            | 0.023    |
| Reactome PI 3K Cascade FGFR4                                                      | 0.686| 1.556            | 0.015    |
| Blanco Meilo Beta Interferon_Treated Bronchial Epithelial Cells_Up                | 0.595| 1.556            | 0.013    |
| Reactome Rhov Gtpase Cycle                                                        | 0.614| 1.555            | 0.027    |
| Valk_Aml Cluster_10                                                               | 0.768| 1.554            | 0.011    |
| Sana Tnf Signaling Up                                                             | 0.690| 1.554            | 0.023    |
| Foster Tolerant Macrophage_Dn                                                     | 0.575| 1.554            | 0.009    |
| Kim All Disorders Oligodendrocyte Number Corr_Dn                                  | 0.673| 1.554            | 0.008    |
| Hahtola Mycosis Fungoides Cd4_Dn                                                  | 0.490| 1.553            | 0.042    |
| WP Development and Heterogeneity of The ILC Family                                | 0.699| 1.551            | 0.010    |
| Osmann Bladder Cancer Up                                                          | 0.520| 1.550            | 0.034    |
| Mili Pseudopodia_Chemotaxis_Up                                                    | 0.500| 1.550            | 0.008    |
| Bild Src Oncogenic Signature                                                      | 0.553| 1.548            | 0.007    |
| Wang Response to Bexarotene_Dn                                                    | 0.615| 1.547            | 0.014    |
| Traynor Rett Syndrome_Up                                                          | 0.676| 1.545            | 0.013    |
| Pid Avb3_Opn Pathway                                                              | 0.633| 1.544            | 0.028    |
| Gargalovic Response to Oxidized Phospholipids_Brown_Up                           | 0.665| 1.543            | 0.016    |
| Lee Differentiating T Lymphocyte                                                  | 0.546| 1.542            | 0.036    |
| Ono Foxp3 Targets_Dn                                                              | 0.666| 1.542            | 0.027    |
| Biocarta TALL1 Pathway                                                            | 0.708| 1.541            | 0.023    |
| Douglas Bmi1 Targets_Dn                                                           | 0.468| 1.541            | 0.010    |
| Zhang Response to Ikk Inhibitor_and_Tnf_Up                                        | 0.658| 1.540            | 0.023    |
| Liang Hematopoiesis Stem Cell Number Large_Vs_Tiny_Dn                             | 0.561| 1.538            | 0.013    |
| Brownie Hcmv Infection 14HR_Up                                                    | 0.499| 1.538            | 0.017    |
| Mcbryan Pubertal Breast 5_6Wk_Dn                                                  | 0.489| 1.538            | 0.012    |
| Shipp Dlbcl Vs Follicular Lymphoma_Dn                                              | 0.634| 1.536            | 0.010    |
| Kegg Rbg 1 Like Receptor Signaling Pathway                                       | 0.517| 1.535            | 0.037    |
| Reactome Apoptotic Cleavage of Cellular Proteins                                | 0.576| 1.534            | 0.015    |
| Debiiasi Apoptosis By Reovirus Infection Up                                      | 0.571| 1.532            | 0.033    |
| Zhan Multiple Myeloma Pr_Dn                                                       | 0.609| 1.531            | 0.020    |
| Howlin Cited1 Targets_1_Dn                                                        | 0.618| 1.531            | 0.020    |
| Reactome Regulation Of Kit Signaling                                              | 0.761| 1.530            | 0.027    |
| Kenny_Ctnnb1 Targets_Dn                                                            | 0.591| 1.529            | 0.025    |
| Pid Nfkappaab Canonical Pathway                                                    | 0.667| 1.528            | 0.036    |
| Blanco Meilo Human Parainfluenza Virus 3 Infection_A594_Cells_Up                  | 0.622| 1.528            | 0.029    |
| Graham Cml Quiescent Vs Cml Dividing Up                                           | 0.808| 1.528            | 0.021    |
| Reactome Tie2 Signaling                                                           | 0.626| 1.527            | 0.020    |
| Baldwin Prkci Targets_Dn                                                           | 0.591| 1.525            | 0.016    |
| Chiang Liver Cancer Subclass Unannotated_Up                                     | 0.553| 1.525            | 0.009    |
| Martinez Response to Trabectedin_Dn                                               | 0.504| 1.524            | 0.040    |
| Scheideretz_Ikk Interacting Proteins                                              | 0.550| 1.523            | 0.033    |
| Reactome Negative Regulation Of Fgfr2_Signaling                                 | 0.547| 1.523            | 0.025    |
| Shi Sparc Targets_Up                                                              | 0.647| 1.523            | 0.018    |
| Gargalovic Response to Oxidized Phospholipids Red_Dn                             | 0.607| 1.522            | 0.028    |
| Dazard Response to Uv_Scc_Dn                                                       | 0.550| 1.521            | 0.028    |
| Mahajan Response to Ii1a_Up                                                       | 0.653| 1.521            | 0.020    |
| Gargalovic Response to Oxidized Phospholipids Yellow_Up                         | 0.650| 1.517            | 0.032    |
| Wp Interactions Between Immune Cells And Micr Onas In Tumor Micr                  | 0.722| 1.517            | 0.033    |
| Nagashima Nrg1_Signaling_Dn                                                       | 0.576| 1.516            | 0.016    |
| Valk_Aml Cluster_15                                                                | 0.778| 1.516            | 0.024    |
| Wu_Hbx Targets_2_Dn                                                               | 0.683| 1.514            | 0.033    |
| Chiaretti T All Refractory To Therapy                                            | 0.660| 1.513            | 0.015    |
| Jaatinen Hematopoietic Stem Cell Therapy                                         | 0.613| 1.513            | 0.019    |
**CALCR** in childhood AML

| Pathway Description                                      | Score | P Value | Fold Change |
|---------------------------------------------------------|-------|---------|-------------|
| DURCHDEWALD_SKIN_CARCINOGENESIS_DN                      | 0.522 | 1.513   | 0.015       |
| PID_CD8_TCR_DOWNSTREAM_PATHWAY                          | 0.629 | 1.509   | 0.049       |
| PID_P38_ALPHA_BETA_PATHWAY                              | 0.606 | 1.508   | 0.029       |
| REACTOME_RETROGRADE_TRANSPORT_AT_THE_TRANS_GOLGI_NETWORK| 0.470 | 1.507   | 0.027       |
| SENESE_HDAC1_TARGETS_UP                                 | 0.534 | 1.507   | 0.030       |
| PID_ARF6_PATHWAY                                        | 0.609 | 1.504   | 0.016       |
| REACTOME_REGULATION_OF_SIGNALING_BY_CBL                 | 0.572 | 1.503   | 0.043       |
| HU_GENOTOXIN_ACTION DIRECT VS INDIRECT 4HR              | 0.554 | 1.502   | 0.012       |
| SU_THYMUS                                               | 0.763 | 1.501   | 0.034       |
| DORSAM_HOX9_TARGETS_UP                                  | 0.551 | 1.501   | 0.037       |
| FRASOR_RESPONSE_TO_SERM_OR_FULVESTRASTR_1J_UP          | 0.646 | 1.500   | 0.032       |
| SASSON_RESPONSE_TO_GONADOTROPHINS_DN                    | 0.544 | 1.500   | 0.016       |
| ENK_UV_RESPONSE_KERATINOCYTE_DN                        | 0.467 | 1.499   | 0.033       |
| SESTO_RESPONSE_TO_UVC5                                  | 0.618 | 1.499   | 0.044       |
| TERAMOTO_OPN_TARGETS_CLUSTER_7                         | 0.620 | 1.497   | 0.016       |
| SPIRA_SMOKERS_LUNG_CANCER_UP                            | 0.660 | 1.496   | 0.043       |
| BLANCO_MELO_COVID19_SARS_COV_2_INFECTION_CALU3 CELLS_UP | 0.602 | 1.495   | 0.022       |
| ZHANG_RESPONSE_TO_CANTHARIDIN_DN                        | 0.739 | 1.495   | 0.049       |
| KEGG_NODLIKE_RECEPTOR_SIGNALING_PATHWAY                 | 0.610 | 1.494   | 0.042       |
| GAVIN_FOXP3_TARGETS_CLUSTER_T4                          | 0.550 | 1.494   | 0.025       |
| GAVIN_FOXP3_TARGETS_CLUSTER_P4                          | 0.575 | 1.493   | 0.013       |
| WP_THYMIC_STROMAL_LYMPHOPOIETIN_TSLP_SIGNALING_PATHWAY  | 0.599 | 1.493   | 0.043       |
| MONNIER_POSTRADIATION_TUMOR_ESCAPE_UP                   | 0.424 | 1.490   | 0.008       |
| OSMAN_BLADDER_CANCER_DN                                 | 0.404 | 1.490   | 0.022       |
| ZWANG_EGF_PERSISTENTLY_UP                               | 0.561 | 1.490   | 0.022       |
| GAVIN_IL2_RESPONSIVE_FOXP3_TARGETS_UP                   | 0.645 | 1.489   | 0.029       |
| REACTOME_NEGATIVE_REGULATION_OF_THE_PI3K_AKT_NETWORK    | 0.537 | 1.489   | 0.012       |
| TAKEDA_TARGETS_OF_NUP98_HOX9_FUSION_10D_UP              | 0.613 | 1.489   | 0.007       |
| RIZ_ERYTHROID_DIFFERENTIATION_6HR                       | 0.643 | 1.488   | 0.028       |
| GHANDHI_BYSTANDER_IRRADIATION_UP                         | 0.684 | 1.488   | 0.031       |
| REACTOME_NEGATIVE_REGULATION_OF_FGFR4_SIGNALING         | 0.538 | 1.486   | 0.037       |
| WANG_RESPONSE_TO_FORSKOLIN_UP                            | 0.584 | 1.485   | 0.036       |
| BLANCO_MELO_RESPIRATORY_SYNCYTIAL_VIRUS_INFECTION_A594.Cells_UP | 0.613 | 1.484   | 0.029       |
| LEE_RECENT_THYMIC_EMMIGRANT                             | 0.501 | 1.482   | 0.022       |
| REACTOME_SIGNALING_BY_TYPE_1_INSULINLIKE_GROWTH_FACTOR_1 | 0.557 | 1.482   | 0.022       |
| CHIARETTI_ACUTE_LYMPHOBLASTIC_LEUKEMIA_ZAP70            | 0.526 | 1.482   | 0.025       |
| BERENJENO_TRANSFORMED_BY_RHOA_FOREVER_DN                | 0.712 | 1.482   | 0.029       |
| FERRARI_RESPONSE_TO_FENRETINIDE_UP                      | 0.762 | 1.481   | 0.035       |
| RODRIGUES_THYROID_CARCINOMA_DN                          | 0.597 | 1.480   | 0.024       |
| OKUMURA_INFLAMMATORY_RESPONSE_LPS                       | 0.532 | 1.480   | 0.014       |
| KAMIKUBO_MYELOID_MN1_NETWORK                            | 0.702 | 1.480   | 0.041       |
| BILD_CTNBN1_ONCOGENIC_NAME                              | 0.570 | 1.478   | 0.040       |
| TENEDINI_MEGAKARYOCYTE_MARKERS                          | 0.616 | 1.478   | 0.034       |
| VALK_AML_WITH_EVII                                     | 0.746 | 1.478   | 0.027       |
| ZHAN_MULTIPLE_MYELOMA_HP_UP                             | 0.529 | 1.477   | 0.025       |
| REACTOME_Digestion_and_absorption                       | 0.588 | 1.477   | 0.036       |
| BIOCARTA_EDG1_PATHWAY                                   | 0.623 | 1.476   | 0.031       |
| PID_PK5_NTR_PATHWAY                                     | 0.483 | 1.476   | 0.018       |
| REACTOME_PI30CAS_LINKAGE_TO_MAPK_SIGNALING_FOR_INTEGRINS| 0.754 | 1.475   | 0.037       |
| WP_PREGNANE_X_RECEPTOR_PATHWAY                          | 0.572 | 1.475   | 0.031       |
| ONO_AML1_TARGETS_DN                                     | 0.630 | 1.474   | 0.042       |
| MULLIGHAN_NPM1_MUTATED_SIGNATURE_2_UP                   | 0.559 | 1.474   | 0.041       |
| REACTOME_CD28_CO_STIMULATION                            | 0.590 | 1.474   | 0.040       |
| ALCALAY_AML_BY_NPM1_LOCALIZATION_UP                     | 0.706 | 1.474   | 0.041       |
| ZWANG_CLASS_3_TRANSIENTLY_INDUCED_BY_EGF                | 0.607 | 1.472   | 0.040       |
| YAGI_AML_WITH_INV16_TRANSLOCATION                      | 0.460 | 1.472   | 0.015       |
| REACTOME_PI3K Cascades FGF83                           | 0.672 | 1.471   | 0.046       |
| WP_NCRNAS_INVOLVED_INSTAT3_SIGNALING_INHEPATOCELLULARCARCINOMA | 0.669 | 1.470   | 0.045       |
| BASAKI_YBX1_TARGETS_DN                                  | 0.500 | 1.468   | 0.021       |
| TONKS_TARGETS_OF_RUNX1_RUNXIT1_MONOCYTE_DN              | 0.643 | 1.468   | 0.041       |
| WP_SARS_C02_INNATE_IMMUNITY EVASION AND CELLSPECIFIC_IMMUNE_RESPON | 0.627 | 1.467   | 0.041       |
| PID_INTEGRIN_A4B1_PATHWAY                               | 0.624 | 1.467   | 0.045       |
| GINESTIER_BREAST_CANCER_20Q13_AMPLIFICATION_UP          | 0.470 | 1.466   | 0.020       |
| Pathway Description | Z-Score | P-value | Adjusted P-value |
|---------------------|---------|---------|-----------------|
| CALCRL in childhood AML |         |         |                 |
| PID ANGIOPOETIN RECEPTOR_PATHWAY | 0.545 | 1.466 | 0.035 |
| STEARMAN LUNG CANCER_EARLY VS_LATE_UP | 0.465 | 1.466 | 0.039 |
| BROWNE HCMV INFECTION 4HR_UP | 0.657 | 1.465 | 0.043 |
| SASSON_RESPONSE_TO_FORSKOLIN_DN | 0.522 | 1.464 | 0.023 |
| HIRSCH CELLULARTRANSFORMATION_SIGNATURE_DN | 0.505 | 1.464 | 0.020 |
| GENTILE UV_RESPONSE_CLUSTER_D5 | 0.552 | 1.464 | 0.041 |
| REACTOME CONSTITUTIVE_SIGNALING_BY_ABERRANT_PI3K_IN_CANCER | 0.571 | 1.463 | 0.013 |
| WP GLYCEROPHOSPHOLIPID_BIOSYNTHETIC_PATHWAY | 0.492 | 1.463 | 0.031 |
| MARSON FOXP1_TARGETS_STIMULATED_UP | 0.685 | 1.463 | 0.048 |
| ONDER CDH1_TARGETS_1_DN | 0.520 | 1.462 | 0.024 |
| WP NUCLEAR_RECEPTORS_IN_LIPID_METABOLISM_AND_TOXICITY | 0.599 | 1.462 | 0.026 |
| WANG METASTASIS_OF_BREAST_CANCER | 0.652 | 1.461 | 0.031 |
| THUM SYSTOLIC_HEART_FAILURE_DN | 0.473 | 1.460 | 0.015 |
| STAMBOLSKY_RESPONSE_TO_VITAMIN_D3_UP | 0.557 | 1.458 | 0.018 |
| FULCHER INFLAMMATORY_RESPONSE_LECTIN_VS_LPS_DN | 0.545 | 1.458 | 0.041 |
| GRABARCZYK BCL11B_TARGETS_UP | 0.516 | 1.458 | 0.024 |
| REACTOME EICOSANOID_LIGAND_BINDING_RECEPTORS | 0.741 | 1.456 | 0.036 |
| BOSCO TH1_CYTOTOXIC_MODULE | 0.626 | 1.456 | 0.027 |
| CHANDRAN METASTASIS_UP | 0.444 | 1.455 | 0.024 |
| GHANDHI DIRECT_IRRADIATION_UP | 0.631 | 1.454 | 0.037 |
| TING SILENCED_BY_DICER | 0.638 | 1.450 | 0.027 |
| OUILLETTE_CL1_13Q14_DELETION_UP | 0.482 | 1.450 | 0.034 |
| BOYLAN_MULTIPLE_MYELOMA_C_CLUSTER_DN | 0.634 | 1.449 | 0.036 |
| LIU SOX4_TARGETS_UP | 0.493 | 1.448 | 0.031 |
| SAHAI CHRONIC_HEPATITIS_VS_LIVER_CANCER_DN | 0.554 | 1.448 | 0.043 |
| GENTILE UV_RESPONSE_CLUSTER_D8 | 0.578 | 1.448 | 0.046 |
| KIM MYC_AMPLIFICATION_TARGETS_DN | 0.558 | 1.446 | 0.025 |
| COULOUARN TEMPORAL_TGFB1_SIGNATURE_UP | 0.546 | 1.445 | 0.042 |
| HUTTMANN_B_CLL_POOR_SURVIVAL_DN | 0.619 | 1.445 | 0.040 |
| LU IL4_SIGNALING | 0.555 | 1.443 | 0.040 |
| MALTA CURATED_STEMNESS_MARKERS | 0.613 | 1.442 | 0.032 |
| SANA TNF_SIGNALING_DN | 0.594 | 1.441 | 0.033 |
| FINETTI BREAST_CANCERS_KINOME_GRAY | 0.799 | 1.441 | 0.048 |
| WP SMALL_LIGAND_GPCRS | 0.708 | 1.441 | 0.045 |
| ABBUD LIF SIGNALING_1_DN | 0.536 | 1.438 | 0.031 |
| REACTOME SUMOYLATION_OF_INTRACELLULAR_RECEPTORS | 0.546 | 1.437 | 0.038 |
| REACTOME IRS MEDIATED_SIGNALLING | 0.538 | 1.436 | 0.033 |
| AKL HTLV1_INFECTION_DN | 0.565 | 1.431 | 0.037 |
| NIKOLSKY BREAST_CANCER_19Q13.1_AMPLICON | 0.828 | 1.427 | 0.048 |
| SENESE HDAC3_TARGETS_UP | 0.508 | 1.427 | 0.043 |
| TCGA Glioblastoma_COPY_NUMBER_UP | 0.501 | 1.427 | 0.038 |
| TSAI RESPONSE_TO_IONIZING_RADIATION | 0.501 | 1.426 | 0.041 |
| VERNELL RETINOBLASTOMA_PATHWAY_DN | 0.631 | 1.425 | 0.048 |
| WP DRUG_INDUCTION_OF_BILE_ACID_PATHWAY | 0.675 | 1.424 | 0.038 |
| OSWALD HEMATOPOIETIC_STEM_CELL_IN_COLLAGEN_GEL_DN | 0.465 | 1.423 | 0.023 |
| PID ARF6 TRAFFICKING_PATHWAY | 0.534 | 1.423 | 0.030 |
| PID ER NONGENOMIC_PATHWAY | 0.549 | 1.422 | 0.043 |
| LIU CDX2_TARGETS_UP | 0.628 | 1.418 | 0.036 |
| WP G13 SIGNALING_PATHWAY | 0.471 | 1.418 | 0.048 |
| REACTOME INSULIN_RECEPTOR_SIGNALLING CASCADE | 0.518 | 1.417 | 0.042 |
| REACTOME SIGNAL_AMPLIFICATION | 0.549 | 1.417 | 0.038 |
| WARTERS RESPONSE_TO_IR_SKIN | 0.480 | 1.415 | 0.015 |
| GARGALOVIC RESPONSE_TO_OXIDIZED_PHOSPHOLIPIDS_PINK_DN | 0.635 | 1.413 | 0.045 |
| PID FGFR3 PATHWAY | 0.537 | 1.412 | 0.035 |
| HOLLERN MICROACINAR_BREAST_TUMOR_UP | 0.521 | 1.408 | 0.026 |
| RODRIGUES DCC_TARGETS_DN | 0.474 | 1.408 | 0.031 |
| REACTOME PI3K_AKT_SIGNALING_IN_CANCER | 0.514 | 1.408 | 0.028 |
| WARTERS IR RESPONSE_5G | 0.537 | 1.407 | 0.039 |
| CHARAFE BREAST_CANCER_LUMINAL_VS BASAL_DN | 0.518 | 1.406 | 0.038 |
| PHONG TNF RESPONSE_VIA_PI38_COMPLETE | 0.471 | 1.390 | 0.045 |
| WP 3Q29_COPY_NUMBER_VARIATION_SYNDROME | 0.425 | 1.387 | 0.020 |
| HOFFMANN LARGE_TO_SMALL_PRE_BII_LYMPHOCYTE_DN | 0.505 | 1.380 | 0.037 |
| WAMUNYOKOLI OVARIAN_CANCER_GRADES_1_2_UP | 0.468 | 1.378 | 0.041 |
**CALCRL** in childhood AML

| Enrichment Set                                      | ES  | NES  | NOM P |
|----------------------------------------------------|-----|------|-------|
| TAKEDA_Targets of NUP98 HOXA9 Fusion 16D Up         | 0.578 | 1.370 | 0.039 |
| Reactome Adora2B Mediated Anti-Inflammatory Cytokines Production | 0.469 | 1.367 | 0.034 |
| Corre Multiple Myeloma Up                          | 0.544 | 1.367 | 0.049 |
| Bredemeyer Rag Signaling Not Via ATM Up             | 0.473 | 1.365 | 0.043 |
| Iwanaga Carcinogenesis By Kras Pten Dn             | 0.441 | 1.359 | 0.030 |
| Hoffmann Pre B1 To Large Pre BII Lymphocyte Dn      | 0.498 | 1.357 | 0.042 |
| Wang LMO4 Targets Up                                | 0.372 | 1.332 | 0.031 |

ES, enrichment score; NES, normalized enrichment score; NOM P, nominal p value.
**Supplementary Table 3. Multivariable regression analyses including the LSC17 score.**

| Variables in the model               | OR/HR | 95% CI     | P value |
|--------------------------------------|-------|------------|---------|
| **Complete remission**               |       |            |         |
| LSC17 score: high vs low             | 0.44  | 0.20-0.97  | 0.043   |
| CALCRL expression: high vs low       | 0.60  | 0.28-1.28  | 0.18    |
| **Overall survival**                 |       |            |         |
| LSC17 score: high vs low             | 1.77  | 1.23-2.56  | 0.0022  |
| CALCRL expression: high vs low       | 1.49  | 1.03-2.15  | 0.035   |
| **Event-free survival**              |       |            |         |
| LSC17 score: high vs low             | 1.63  | 1.22-2.20  | 0.0010  |
| CALCRL expression: high vs low       | 1.74  | 1.29-2.36  | 0.0003  |
| **Cumulative incidence of relapse**  |       |            |         |
| LSC17 score: high vs low             | 1.41  | 1.03-1.94  | 0.031   |
| CALCRL expression: high vs low       | 2.06  | 1.49-2.86  | <0.0001 |

Odds ratios (OR) greater or less than 1.0 indicate higher or lower CR rates, respectively, for the first category listed. Hazard ratios (HR) greater or less than 1.0 indicate an increased or decreased risk, respectively, of an event for the first category listed.

Abbreviations: WBC, white blood cell count; CALCRL, calcitonin-receptor like.

§The LSC17 score was calculated and dichotomized as described.1
Supplementary Figures

Supplementary Fig. 1. Optimal cut-point for \textit{CALCRL} gene in pediatric patients with AML. The maximally selected log-rank statistics was performed on the continuous \textit{CALCRL} expression to identify a potential cut-point that separates two groups with different event-free survival distributions. The dashed line represents the optimal cut-point of 0.3282 and the M statistic of 4.24. The adjusted P value was P<0.0001.
Supplementary Fig. 2. Forest plot of the association of \textit{CALCRL} expression on overall survival in selected subgroups of the pediatric TARGET cohort. Hazard ratios (HRs) for high versus low \textit{CALCRL} expression in selected subgroups are shown. The position of the squares represents the unadjusted HRs and the horizontal lines represent the 95% confidence intervals (CI). The size of the squares is proportional to the precision of the estimate. The position diamond and the dotted vertical line represent the overall HR from the entire cohort. The lateral points of the diamond represents the 95% CI. The P values are for interaction of unadjusted hazard ratios by subgroups and represent heterogeneity. Abbreviations: WBC, white blood cell count; HSCT, allogeneic hematopoietic stem cell transplantation; CBF, core-binding factor; NK, normal karyotype; MLL, mixed-lineage leukemia; CK, complex karyotype; FLT3-ITD, internal tandem duplication of the \textit{FLT3} gene; NPM1, nucleophosmin-1.
**CALCRL** in childhood AML

Supplementary Fig. 3. Forest plot of the association of **CALCRL** expression on the risk of relapse in selected subgroups of the pediatric TARGET cohort. Hazard ratios (HRs) for high versus low **CALCRL** expression in selected subgroups are shown. The position of the squares represents the unadjusted HRs and the horizontal lines represent the 95% confidence intervals (CI). The size of the squares is proportional to the precision of the estimate. The position diamond and the dotted vertical line represent the overall HR from the entire cohort. The lateral points of the diamond represents the 95% CI. The P values are for interaction of unadjusted hazard ratios by subgroups and represent heterogeneity. Abbreviations: WBC, white blood cell count; HSCT, allogeneic hematopoietic stem cell transplantation; CBF, core-binding factor; NK, normal karyotype; MLL, mixed-lineage leukemia; CK, complex karyotype; FLT3-ITD, internal tandem duplication of the **FLT3** gene; **NPM1**, nucleophosmin-1.

| Subgroup | low no. of relapses / no. of patients (%) | high no. of relapses / no. of patients (%) | HR (95% CI) | P Value |
|----------|------------------------------------------|------------------------------------------|------------|--------|
| Age      | infant 23/47 (33.2) / 10/13 (76.9)        |                                          | 2.04 (0.97–4.30) | 0.34   |
|          | child 51/114 (44.7) / 36/50 (72.0)        |                                          | 2.60 (1.88–4.42) |        |
|          | adolescent 19/45 (42.2) / 13/18 (71.1)    |                                          | 1.34 (0.64–2.81) |        |
| Sex      | male 42/102 (41.2) / 32/69 (46.4)         |                                          | 2.30 (1.45–3.66) | 0.78   |
|          | female 53/101 (52.3) / 28/52 (53.8)       |                                          | 2.11 (1.20–3.72) |        |
| WBC      | <50 x 10⁹ 59/114 (46.5) / 32/40 (80.0)   |                                          | 2.71 (1.77–4.02) | 0.15   |
|          | ≥50 x 10⁹ 42/89 (47.2) / 25/41 (61.0)     |                                          | 1.84 (1.00–3.07) |        |
| Trial    | AAML, 01P 17/74 (28.6) / 10/63 (62.5)     |                                          | 1.68 (0.77–3.68) | 0.56   |
|          | AAML, 05P 63/132 (48.2) / 37/51 (72.5)    |                                          | 2.54 (1.56–4.07) |        |
|          | CCG-2961 17/27 (63.0) / 10/14 (71.4)      |                                          | 1.87 (0.85–4.09) | 0.069  |
|          | yes 5/22 (22.7) / 10/13 (76.9)            |                                          | 4.59 (1.54–13.62)| 0.040  |
|          | no 90/159 (56.6) / 47/94 (80.7)           |                                          | 1.96 (0.97–3.98) |        |
| Risk group | low 32/89 (36.0) / 20/27 (74.1)        |                                          | 2.54 (1.45–4.46) | 0.57   |
|          | standard 52/86 (60.5) / 24/34 (70.6)      |                                          | 1.36 (0.83–2.21) |        |
|          | high 6/16 (37.5) / 8/13 (61.5)            |                                          | 4.55 (1.50–13.79)|        |
| CBF      | yes 8/18 (43.3) / 18/22 (81.8)           |                                          | 2.38 (1.30–4.34) | 0.77   |
|          | no 63/128 (49.2) / 34/52 (65.4)           |                                          | 1.99 (1.31–3.04) |        |
| NK       | yes 18/47 (38.3) / 13/23 (55.6)           |                                          | 2.00 (0.98–4.10) |        |
|          | no 73/156 (50.0) / 39/51 (76.5)           |                                          | 2.24 (1.51–3.33) |        |
| MLL      | yes 24/35 (68.6) / 3/4 (75.0)             |                                          | 1.88 (0.56–6.26) | 0.79   |
|          | no 67/158 (42.4) / 49/70 (70.0)           |                                          | 2.38 (1.64–4.36) |        |
| CK       | yes 11/15 (73.3) / 3/4 (75.0)             |                                          | 1.02 (0.28–4.73) | 0.14   |
|          | no 80/178 (44.9) / 49/70 (70.0)           |                                          | 2.29 (1.60–3.38) | 0.066  |
| FLT3-ITD | neg 87/181 (48.3) / 40/56 (71.4)         |                                          | 1.79 (1.23–2.61) |        |
|          | pos 8/22 (36.4) / 17/25 (68.0)           |                                          | 4.44 (1.85–10.65)|        |
| NPM1     | wt 90/185 (48.6) / 50/70 (71.4)           |                                          | 1.20 (1.35–3.13) | 0.076  |
|          | mut 2/12 (16.7) / 4/7 (57.1)              |                                          | 3.51 (0.64–19.34)|        |

All patients 95/203 (46.8) / 57/81 (70.4)
Supplementary Fig. 4. LSC17 score and survival in the pediatric TARGET cohort. Event-free survival (A), overall survival (B) and cumulative incidence of relapse (C) according to the dichotomized LSC17 score.
References

1. Ng SW, Mitchell A, Kennedy JA, et al. A 17-gene stemness score for rapid determination of risk in acute leukaemia. Nature. 2016;540(7633):433-437.