

Supplementary Table 1. Cytogenetic classifications at the time of ALL diagnosis for the patients in the training and test sets.

	Training set	Test set
<i>B-ALL, NOS</i>	26.7% (n = 153)	23.2% (n = 44)
<i>B-ALL, hyperploid</i>	24.6% (n = 141)	28.4% (n = 54)
<i>B-ALL with t(12;21)(p13.2;q22.1)/ETV6::RUNX1</i>	21.1% (n = 121)	22.6% (n = 43)
<i>T-ALL</i>	13.4% (n = 77)	12.6% (n = 24)
<i>B-ALL with t(1;19)(q23.3;p13.3)/TCF3::PBX1</i>	3.7% (n = 21)	0% (n = 0)
<i>B-ALL with t(v;11q23.3)/KMT2A rearranged</i>	3.3% (n = 19)	4.7% (n = 9)
<i>B-ALL, with PAX5 alteration</i>	3.0% (n = 17)	3.2% (n = 6)
<i>B-ALL with t(9;22)(q34.1;q11.2)/BCR::ABL1</i>	2.6% (n = 15)	2.1% (n = 4)
<i>B-ALL with iAMP21</i>	1.2% (n = 7)	2.6% (n = 5)
<i>B-ALL, hypoploid</i>	0.3% (n = 2)	0.5% (n = 1)

Supplementary Table 2. C-indexes of the different random forest models evaluated for the prediction of RFS and OS.

OS predictors				
Q-value	HR filter	Correlation Filter	Training set c-index	Test set c-index
0.05	Yes	No	0.7383	0.7374
0.05	No	No	0.7388	0.7256
0.01	Yes	No	0.7245	0.7146
0.01	No	No	0.7219	0.7189
0.05	Yes	Yes	0.7469	0.759
0.05	No	Yes	0.751	0.726
0.01	Yes	Yes	0.7082	0.6905
0.01	No	Yes	0.7141	0.7141

RFS predictors				
Q-value		Correlation Filter	Training set c-index	Test set c-index
0.05	Yes	No	0.6408	0.6856
0.05	No	No	0.6408	0.6856
0.01	Yes	No	0.6329	0.668
0.01	No	No	0.6329	0.668

Supplementary Table 3. Variable importance values for each of the CpGs in the relapse risk predictor (RRP). CpGs are listed in decreasing order of importance.

ID	Order	Variable Importance
<i>cg25663770</i>	1	0.06554844
<i>cg18358754</i>	2	0.059755976
<i>cg20324356</i>	3	0.055948684
<i>cg17209692</i>	4	0.046814949
<i>cg22535729</i>	5	0.046196853
<i>cg14396214</i>	6	0.044118723
<i>cg03446203</i>	7	0.041276727
<i>cg18076500</i>	8	0.032943851
<i>cg21173721</i>	9	0.028398854
<i>cg16267059</i>	10	0.027563885
<i>cg08445782</i>	11	0.02581552
<i>cg00046913</i>	12	0.02409957
<i>cg08025954</i>	13	0.022245443
<i>cg23672291</i>	14	0.021704871
<i>cg04956471</i>	15	0.018572842
<i>cg10286363</i>	16	0.014819689

Supplementary Table 4. Patient distribution across the low- and high- relapse risk or mortality risk predictor (RRP/MRP) groups after applying cut-offs on the train, test and independent datasets. a) Low and high-RRP groups in response to relapse as outcome, b) low and high-MRP groups in response to relapse as outcome and c) low and high-MRP groups in response to death as outcome. Univariate cox regression was conducted to assess the effect of the RRP/MRP-based dichotomization on patient outcome.

RRP cut-off on relapse data	Train dataset (n = 573)						Test dataset (n = 190)			
	n patients	% patients	n relapses	within group % relapses	COX regression HR*	p-value	n patients	% patients	n relapses	within group % relapses
a) low-RRP	436	76.1	74	17	Reference	-	150	78.9	25	16.7
high-RRP	137	23.9	55	40.1	2.982 (95% CI: 2.102-4.229)	8.98 x 10 ⁻¹⁰	40	21.1	18	45
Total	573	100	129				190	100	43	

MRP cut-off on relapse data	Train dataset (n = 573)						Test dataset (n = 199)			
	n patients	% patients	n relapses	within group % relapses	COX regression HR*	p-value	n patients	% patients	n relapses	within group % relapses
b)										
low-MRP	472	82.4	98	20.8	Reference	-	159	83.7	31	19.5
high-MRP	101	17.6	31	30.7	2.182 (95% CI: 1.456-3.27)	0.000157	31	16.3	12	38.7
Total	573	100	129				190	100	43	

	MRP cut-off on mortality data	Train dataset (n = 573)					Test dataset (n = 190)			
		n patients	% patients	n deaths	within group % deaths	COX regression HR*	p-value	n patients	% patients	n deaths
c)		18	3%	1	5%	0.0001	10	5%	1	10%

low-MRP	472	82.4	53	11.2	Reference	-	159	83.7	15	9.4
high-MRP	101	17.6	44	43.6	5.25 (95% CI: 3.516- 7.846)	5.51 x 10 ⁻¹⁶	31	16.3	15	48.4
Total	573	100	97				190	100	30	

*HR:
Hazard
ratio

Supplementary Table 5. Variable importance values for each of the CpGs in the final mortality risk predictor (MRP). Variables are depicted in decreasing order of importance.

ID	Order	Variable Importance
<i>cg27210565</i>	1	0.063527541
<i>cg24536691</i>	2	0.042341039
<i>cg03180426</i>	3	0.041068496
<i>cg02514021</i>	4	0.040311171
<i>cg25149751</i>	5	0.038510061
<i>cg14199423</i>	6	0.034164831
<i>cg13072214</i>	7	0.033705229
<i>cg00470505</i>	8	0.032985824
<i>cg24877510</i>	9	0.03295808
<i>cg04301738</i>	10	0.028867644
<i>cg01911068</i>	11	0.028259842
<i>cg01363662</i>	12	0.027528074
<i>cg12296532</i>	13	0.026475847
<i>cg11096441</i>	14	0.02633762
<i>cg14911521</i>	15	0.025627303
<i>cg27177997</i>	16	0.024900512
<i>cg27377289</i>	17	0.024210814
<i>cg03033176</i>	18	0.023074801
<i>cg27139956</i>	19	0.022446827
<i>cg08262220</i>	20	0.021682839
<i>cg26587014</i>	21	0.021155954
<i>cg04444771</i>	22	0.019274253
<i>cg20534287</i>	23	0.019063137
<i>cg17718302</i>	24	0.018363372
<i>cg19675684</i>	25	0.018226099
<i>cg09363128</i>	26	0.018022938
<i>cg16323034</i>	27	0.017824248
<i>cg24496614</i>	28	0.017757746
<i>cg00992239</i>	29	0.017732871
<i>cg10633958</i>	30	0.017696944
<i>cg06454380</i>	31	0.017257257
<i>cg23743428</i>	32	0.016514352
<i>cg16110032</i>	33	0.016450912
<i>cg08374494</i>	34	0.015762679
<i>cg01993576</i>	35	0.015554267
<i>cg00866476</i>	36	0.015148683
<i>cg04384209</i>	37	0.014865501
<i>cg19599529</i>	38	0.014854579
<i>cg03891050</i>	39	0.014626172
<i>cg19726840</i>	40	0.014613516
<i>cg07260003</i>	41	0.014193535
<i>cg00671759</i>	42	0.013626694

<i>cg09926212</i>	43	0.013236141
<i>cg02763617</i>	44	0.012980205
<i>cg07090714</i>	45	0.012969178
<i>cg08576623</i>	46	0.012921712
<i>cg15679331</i>	47	0.012061588
<i>cg23448978</i>	48	0.012011635
<i>cg14541870</i>	49	0.011934702
<i>cg23430664</i>	50	0.011162204
<i>cg02959285</i>	51	0.010143257
<i>cg13901752</i>	52	0.009903484
<i>cg08261702</i>	53	0.006727811

Supplementary Table 6. Revised molecular subtype annotation analyzed by *Krali et al.*

	NOPHO independent set
<i>B-ALL, hyperploid</i>	28.1% (n = 108)
<i>B-ALL with t(12;21)(p13.2;q22.1)/ETV6::RUNX1</i>	26.6% (n = 102)
<i>B-ALL, NOS</i>	26.0% (n = 100)
<i>B-ALL with t(v;11q23.3)/KMT2A rearranged</i>	7.6% (n = 29)
<i>B-ALL with t(1;19)(q23.3;p13.3)/TCF3::PBX1</i>	3.4% (n = 13)
<i>B-ALL, with PAX5 alteration</i>	2.1% (n = 8)
<i>B-ALL, hypoploid</i>	1.8% (n = 7)
<i>B-ALL with iAMP21</i>	1.8% (n = 7)
<i>B-ALL with t(9;22)(q34.1;q11.2)/BCR::ABL1</i>	1.6% (n = 6)
<i>T-ALL</i>	1.0% (n = 4)

Supplementary Table 7. MRP c-indexes of the MRP in the independent dataset.

	Sample Size	C-index
Standard Risk	170	0, 590
Intermediate Risk	126	0, 523
High Risk	66	0.496
Infant	20	0.563