LETTER TO THE EDITOR

Genomic profiling of pediatric hematologic malignancies and diagnosis of cancer predisposition syndromes: tumor-only *versus* paired tumor-normal sequencing

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Supplemental Table 1. Demographics of study cohort

	All N=1190	Tumor testing N=1034	Paired Tumor-Normal testing N=156
Age			
Median age, years (range)	9.2 (0-32)	9.5 (0-32)	6.4 (0-22)
Sex, No (%)			
Female	546(46)	470 (46)	76 (49)
Male	643(54)	563 (55)	80 (51)
Race, No (%)[a]			
White	449 (38)	363 (35)	86 (55)
Black or African American	114 (10)	88 (9)	26 (17)
Asian	34 (3)	25 (2)	9 (6)
Other	160 (13)	125 (2)	35 (22)
Diagnosis, No (%)			
B-ALL	704 (59)	609 (59)	95 (61)
AML/myeloid sarcoma	212 (18)	178 (17)	34 (22)
T-ALL/T-TLL	108 (9)	95 (9)	13 (8)
NHL[b]	68 (6)	63 (6)	5 (3)
Predisposition to MDS/Leukemia[c]	27 (2)	26 (3)	1 (1)
MPN[d]	36 (3)	30 (3)	6(4)
Other[e]	35 (3)	33 (3)	2(1)

[a]432 patients with tumor-only testing missing self-identified race data

[b]NHL=Diffuse large B-cell Lymphoma (DLBCL), Follicular lymphoma, Anaplastic large cell lymphoma (ALCL), Primary mediastinal b-cell lymphoma (PMBCL)

[c]Predisposition to MDS/leukemia= Schwachman Diamond Syndrome, Fanconi anemia, Telomere biology disorder, Severe Congenital Neutropenia with *ELANE* mutation, mosaic Trisomy 8, Diamond-Blackfan anemia, *GATA2* haploinsufficiency syndrome, Noonan Syndrome *PTPN11*, MECOM-associated bone marrow failure syndrome

[d]MPN=Chronic myeloid leukemia (CML), Transient myeloid leukemia of Downs Syndrome (TMD), Juvenile monomyelocytic anemia (JMML)

[e]Other = myelodysplasia (MDS), mixed phenotype acute leukemia/ambiguous lineage leukemia (MPAL/AUL), Hodgkin lymphoma

Supplemental table 2. All variants identified by somatic testing as potentially germline or confirmed as germline on Tumor/Normal (T/N) testing.

Gene	Transcript	Nucleotide	Amino Acid	Mutation type	VAF	Test (somatic or T/N)	Germline Confirmation
TP53	NM_000546.5	c.659A>G	p.Tyr220Cys	missense	0.44	somatic	Unknown
TP53	NM_000546.5	c.1009C>T	p.Arg337Cys	missense	0.51	somatic	Unknown
NRAS	NM_002524.4	c.178G>A	p.Gly60Arg	missense	0.43	somatic	Unknown
DDX41	NM_016222.3	c.4G>T	p.Glu2*	nonsense	0.23	somatic	Unknown
PHF6	NM_032458.2	c.890G>A	p.Cys297Tyr	missense	0.38	somatic	Unknown
RUNX1	NM_001754.4	c.334del	p.Leu112Cysfs*10	frameshift	0.42	somatic	Unknown
PTPN11	NM_002834.4	c.181G>A	p.Asp61Asn	missense	0.45	somatic	Positive
IKZF1	NM_006060.5	c.475A>T	p.Asn159Tyr	missense	0.42	somatic	Unknown
RB1	NM_000321.2	c.1362C>G	p.Tyr454*	nonsense	0.39	somatic	Unknown
GATA2	NM_001145661.1	c.521del	p.Pro174Hisfs*44	frameshift	0.44	somatic	Unknown
RUNX1	NM_001754.4	c.805+1del	p.?	splice_site	0.44	somatic	Unknown
CSF3R	NM_000760.3	c.1640G>A	p.Trp547*	nonsense	0.47	somatic	Unknown
ETV6	NM_001987.4	c.865C>T	p.Gln289*	nonsense	0.49	somatic	Unknown
ETV6	NM_001987.4	c.1014_1020del	p.Arg339Phefs*30	frameshift	0.68	somatic	Unknown
TP53	NM_000546.5	c.614A>G	p.Tyr205Cys	missense	0.83	somatic	Unknown
NF1	NM_001042492.2	c.6855C>A	p.Tyr2285*	nonsense	0.94	somatic	Unknown
RTEL1	NM_016434.3	c.897del	p.Phe299Leufs*10	frameshift	0.39	somatic	Unknown
ETV6	NM_001987.4	c.1202A>G	p.Tyr401Cys	missense	0.61	somatic	Positive
CDKN2A	NM_000077.4	c.377T>A	p.Val126Asp	missense	0.74	somatic	Unknown
ETV6	NM_001987.4	c.416_417del	p.Ser139Tyrfs*14	frameshift	0.54	TN	Positive
GATA2	NM_001145661.1	c.1085G>A	p.Arg362Gln	missense	0.5	TN	Positive
NF1	NM_001042492.2	c.1260+1del	p.?	splice_site	0.25	somatic	Unknown
TP53	NM_000546.5	c.1045G>T	p.Glu349*	nonsense	0.83	somatic	Unknown
CEBPA	NM_004364.4	c.162dup	p.Ile55Hisfs*53	frameshift	0.45	somatic	Unknown
CEBPA	NM_004364.4	c.938_939insTCT	p.Lys313delinsAsnLeu	inframe	0.4	somatic	Unknown
WT1	NM_024426.5	c.1297T>A	p.Cys433Ser	missense	0.76	somatic	Unknown

GATA2	NM_001145661.1	c.989_992dup	p.Leu332Thrfs*53	frameshift	0.41	somatic	Positive
PTPN11	NM_002834.4	c.1504T>C	p.Ser502Pro	missense	0.34	somatic	Unknown
PTPN11	NM_002834.4	c.182A>C	p.Asp61Ala	missense	0.47	somatic	Unknown
RUNX1	NM_001754.4	c.437A>T	p.Asn146Ile	missense	0.45	TN	Positive
CEBPA	NM_004364.5	c.68dup	p.His24Thrfs*136	frameshift	0.34	TN	Positive
JAK2	NM_004972.4	c.2600G>A	p.Arg867Gln	missense	0.37	somatic	Unknown
KRAS	NM_004985.5	c.35G>C	p.Gly12Ala	missense	0.38	somatic	Unknown
SH2B3	NM_005475.3	c.622G>C	p.Glu208Gln	missense	0.52	somatic	Unknown
NF1	NM_001042492.3	c.6855C>A	p.Tyr2285*	nonsense	0.45	somatic	Unknown
TP53	NM_000546.6	c.976G>T	p.Glu326*	nonsense	0.76	somatic	Unknown
PAX5	NM_016734.3	c.295dup	p.Ile99Asnfs*3	frameshift	0.32	somatic	Unknown
GATA2	NM_001145661.1	c.604_624delinsACTT	p.Ala202Thrfs*2	frameshift	0.22	somatic	Positive
JAK3	NM_000215.4	c.307C>T	p.Arg103Cys	missense	0.45	somatic	Unknown
KMT2D	NM_003482.4	c.7228C>T	p.Arg2410*	nonsense	0.41	somatic	Unknown
TP53	NM_000546.6	c.818G>A	p.Arg273His	missense	0.39	somatic	Positive
CREBBP	NM_004380.3	c.4416G>C	p.Trp1472Cys	missense	0.45	somatic	Unknown
PTPN11	NM_002834.5	c.226G>A	p.Glu76Lys	missense	0.43	somatic	Unknown
IKZF1	NM_006060.6	c.331C>T	p.Arg111*	nonsense	0.48	TN	Positive
ETV6	NM_001987.5	c.163+1G>A	p.?	splice_site	0.48	somatic	Unknown
NF1	NM_001042492.2	c.205-2A>T	p.?	splice_site	0.36	somatic	Unknown
NF1	NM_001042492.2	c.2033dupC	p.I679Dfs*21	frameshift	0.35	somatic	Unknown
NF1	NM_001042492.2	c.7909C>T	p.R2637*	nonsense	0.21	somatic	Unknown
PTPN11	NM_002834.4	c.214G>A	p.A72T	missense	0.41	somatic	Unknown
PAX5	NM_016734.2	c.749dupT	p.T251Hfs*38	frameshift	0.45	somatic	Unknown
MSH6	NM_000179.2	c.3261dupC	p.F1088Lfs*5	frameshift	0.46	somatic	Negative
TP53	NM_000546.5	c.646G>A	p.V216M	missense	0.91	somatic	Negative
MSH2	NM_000251.2	c.1861C>T	p.R621*	nonsense	0.87	somatic	Unknown
TP53	NM_000546.5	c.743G>A	p.R248Q	missense	0.88	somatic	Unknown
TP53	NM_000546.5	c.789_833delinsCCCT	p.Leu264Profs*28	frameshift	0.78	somatic	Unknown
IKZF1	NM_006060.5	c.568_583delinsTTTA	p.G190_H195delinsFN	inframe	0.48	somatic	Unknown
KMT2D	NM_003482.3	c.4163G>T	p.Arg1388Leu	missense	0.55	somatic	Unknown

MPL	NM_005373.2	c.117G>T	p.Lys39Asn	missense	0.48	somatic	Unknown
JAK2	NM_004972.3	c.3188G>A	p.Arg1063His	missense	0.43	somatic	Unknown
PTPN11	NM_002834.4	c.923A>G	p.Asn308Ser	missense	0.46	somatic	Unknown
MPL	NM_005373.2	c.407C>T	p.Pro136Leu	missense	0.43	somatic	Unknown
TP53	NM_000546.5	c.827C>A	p.Ala276Asp	missense	0.91	somatic	Unknown
CSFR3	NM_000760.3	c.2221C>T	p.Gln741*	nonsense	0.78	somatic	Negative
RUNX1	NM_001754.4	c.484A>G	p.Arg162Gly	missense	0.38	somatic	Negative
CBL	NM_005188.3	c.1141T>C	p.Cys381Arg	missense	0.98	somatic	Positive
NF1	NM_001042492.2	c.2709G>A	p.Val903Val	missense	0.27	somatic	Unknown
NF1	NM_001042492.2	c.6147+1G>A	p.?	splice_site	0.2	somatic	Unknown
PTPN11	NM_002834.4	c.181G>T	p.Asp61Tyr	missense	0.43	somatic	Negative
TP53	NM_000546.5	c.733G>A	p.Gly245Ser	missense	0.51	somatic	Unknown
PAX5	NM_016734.2	c.910+1G>A	p.?	splice_site	0.48	somatic	Unknown
ETV6	NM_001987.4	c.463+1G>A	p.?	splice_site	0.6	somatic	Unknown
IKZF1	NM_006060.5	c.484C>T	p.Arg162Trp	missense	0.9	somatic	Negative
CBL	NM_005188.3	c.1100A>C	p.Gln367Pro	missense	0.92	somatic	Negative
TP53	NM_000546.5	c.743G>A	p.Arg248Gln	missense	0.2	somatic	Negative
CEBPA	NM_004364.4	c.52_61dup	p.Ser21Thrfs*90	frameshift	0.23	somatic	Unknown
PAX5	NM_016734.2	c.239C>G	p.Pro80Arg	missense	0.38	somatic	Negative
PAX5	NM_016734.2	c.103del	p.Asp35Metfs*2	frameshift	0.41	somatic	Negative
ETV6	NM_001987.4	c.613dup	p.Leu205Profs*12	frameshift	0.39	somatic	Negative
DNMT3A	NM_022552.4	c.2645G>A	p.Arg882His	missense	0.45	somatic	Positive
TP53	NM_000546.5	NA	whole_gene	deletion	1	somatic	Positive
NF1	NM_001042492.2	c.5327C>A	p.Ser1776*	nonsense	0.89	somatic	Unknown
SH2B3	NM_005475.2	c.622G>C	p.Glu208Gln	missense	0.95	somatic	Unknown
DNM2	NM_001005360.2	c.1684_1686del	p.Lys562del	inframe	0.33	somatic	Unknown
GATA2	NM_001145661.1	c.1085G>A	p.Arg362Gln	missense	0.51	somatic	Unknown
DDX41	NM_016222.3	c.844C>T	p.Arg282Cys	missense	0.47	somatic	Unknown
TP53	NM_000546.5	c.524G>A	p.Arg175His	missense	0.9	somatic	Unknown
PHF6	NM_032458.2	c.494del	p.Gly165Glufs*53	frameshift	0.51	somatic	Unknown
IKZF1	NM_006060.5	c.91A>G	p.Met31Val	missense	0.5	somatic	Unknown

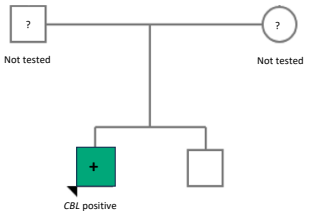
DNMT3A	NM_022552.4	c.2645G>A	p.Arg882His	missense	0.47	somatic	Unknown
KMT2D	NM_003482.3	c.10441-1G>A	p.?	splice_site	0.44	somatic	Unknown
EP300	NM_001429.3	c.5403C>A	p.Cys1801*	nonsense	0.39	somatic	Unknown
NOTCH1	NM_017617.4	c.5033T>C	p.Leu1678Pro	missense	0.48	somatic	Unknown
PHF6	NM_032458.2	c.820C>T	p.Arg274*	nonsense	0.38	somatic	Unknown
TP53	NM_000546.5	c.916C>T	p.Arg306*	nonsense	0.36	somatic	Negative
TP53	NM_000546.5	c.1024C>T	p.Arg342*	nonsense	0.26	somatic	Negative
TP53	NM_000546.5	c.646G>A	p.Val216Met	missense	0.97	somatic	Negative
MPL	NM_005373.2	c.815G>A	p.Trp272*	nonsense	0.46	somatic	Unknown
RELN	NM_005045.3	c.8433del	p.Pro2812Glnfs*16	frameshift	0.46	somatic	Unknown
PTPN11	NM_002834.4	c.226G>A	p.Glu76Lys	missense	0.43	somatic	Unknown
ETV6	NM_001987.4	c.460_461dup	p.Asp155Lysfs*55	frameshift	0.15	somatic	Unknown
NF1	NM_001042492.2	c.7271_7272del	p.Arg2424Lysfs*3	frameshift	0.34	somatic	Unknown
NF1	NM_001042492.2	c.7271_7272del	p.Arg2424Lysfs*3	frameshift	0.34	somatic	Unknown
TP53	NM_000546.5	c.742C>T	p.Arg248Trp	missense	0.38	somatic	Unknown
TP53	NM_000546.5	c.742C>T	p.Arg248Trp	missense	0.38	somatic	Unknown
CREBBP	NM_004380.2	c.1409T>A	p.Leu470*	nonsense	0.35	somatic	Unknown
TP53	NM_000546.5	c.818G>A	p.Arg273His	missense	0.62	somatic	Negative
BCL11B	NM_138576.3	c.1942_1956delinsCCGGTCGCATT	p.Gly648Profs*74	frameshift	0.38	somatic	Unknown
JAK3	NM_000215.3	c.1718C>T	p.Ala573Val	missense	0.43	somatic	Unknown
NOTCH1	NM_017617.4	c.7072G>A	p.Ala2358Thr	missense	0.53	somatic	Unknown
NOTCH1	NM_017617.4	c.6392del	p.Gly2131Alafs*117	frameshift	0.41	somatic	Unknown
KRAS	NM_004985.4	c.187G>A	p.Glu63Lys	missense	0.89	somatic	Negative
IKZF1	NM_006060.5	c.475A>T	p.Asn159Tyr	missense	0.47	somatic	Negative
CBL	NM_005188.3	c.1228-2A>G	p.?	splice_site	0.9	somatic	Negative
TP53	NM_000546.5	c.818G>A	p.Arg273His	missense	0.37	somatic	Negative
NF1	NM_001042492.2	c.7189G>T	p.Gly2397Trp	missense	0.78	somatic	Unknown
PTPN11	NM_002834.4	c.215C>T	p.Ala72Val	missense	0.44	somatic	Unknown
CEBPA	NM_004364.4	c.333_334dup	p.Pro112Argfs*49	frameshift	0.48	somatic	Negative
CEBPA	NM_004364.4	c.941_942ins15	p.Val314_Leu315insSerSerGlnLysVal	inframe	0.34	somatic	Negative
CEBPA	NM_004364.4	c.937_939dup	p.Lys313dup	inframe	0.38	somatic	Unknown

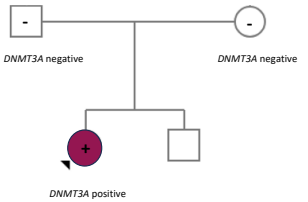
CEBPA	NM_004364.4	c.245del	p.Phe82Serfs*78	frameshift	0.4	somatic	Unknown
MSH2	NM_000251.2	NA	exon_12_16	deletion	0.5	somatic	Unknown
CSF3R	NM_000760.3	c.799del	p.Glu267Serfs*61	frameshift	0.48	somatic	Unknown
IKZF1	NM_006060.5	c.484C>T	p.Arg162Trp	missense	0.44	somatic	Unknown
JAK2	NM_004972.3	c.2047A>G	p.Arg683Gly	missense	0.38	somatic	Unknown
PAX5	NM_016734.2	c.239C>G	p.Pro80Arg	missense	0.44	somatic	Unknown
SETD2	NM_014159.6	c.5735T>A	p.Leu1912*	nonsense	0.73	somatic	Unknown
TP53	NM_000546.5	c.1009C>T	p.Arg337Cys	missense	0.11	somatic	Unknown
TP53	NM_000546.5	c.846_847insGCCCAGG	p.Arg283Alafs*25	frameshift	0.68	somatic	Negative
TP53	NM_000546.5	c.716A>G	p.Asn239Ser	missense	0.53	somatic	Unknown
TP53	NM_000546.5	c.707A>G	p.Tyr236Cys	missense	0.43	somatic	Unknown
CREBBP	NM_004380.2	c.5039_5041del	p.Ser1680del	inframe	0.41	somatic	Unknown
KMT2D	NM_003482.3	c.15784+2T>C	p.?	splice_site	0.44	somatic	Unknown
MSH2	NM_000251.2	c.2087C>T	p.Pro696Leu	missense	0.47	somatic	Positive
TP53	NM_000546.5	c.845G>C	p.Arg282Pro	missense	0.81	somatic	Unknown
TP53	NM_000546.5	c.670G>A	p.Glu224Lys	missense	0.36	somatic	Negative
TP53	NM_000546.5	c.738G>A	p.Met246Ile	missense	0.65	somatic	Negative
NF1	NM_001042492.2	NA	exon_16_36	deletion	0.5	somatic	Unknown
TP53	NM_000546.5	c.743G>C	p.Arg248Pro	missense	0.7	somatic	Unknown
GATA2	NM_001145661.1	c.1085G>A	p.Arg362Gln	missense	0.29	somatic	Unknown
RUNX1	NM_001754.4	c.634_635insT	p.Asp212Valfs*16	frameshift	0.2	somatic	Unknown
RUNX1	NM_001754.4	NA	exon_4_7	deletion	0.5	somatic	Unknown
TP53	NM_000546.5	c.718A>G	p.Ser240Gly	missense	0.7	somatic	Unknown
CDKN2A	NM_000077.4	c.172C>T	p.Arg58*	nonsense	0.41	somatic	Negative
TP53	NM_000546.5	c.743G>A	p.Arg248Gln	missense	0.3	somatic	Negative
TP53	NM_000546.5	c.817C>T	p.Arg273Cys	missense	0.39	somatic	Negative
CREBBP	NM_004380.2	c.4361T>G	p.Leu1454Arg	missense	0.67	somatic	Unknown
MSH6	NM_000179.2	c.1483C>T	p.Arg495*	nonsense	0.32	somatic	Unknown
MSH6	NM_000179.2	c.1444C>T	p.Arg482*	nonsense	0.3	somatic	Unknown
TP53	NM_000546.5	c.847delinsGAGGCGA	p.Arg283delinsGluAlaSer	inframe	0.44	somatic	Unknown
MSH6	NM_000179.2	c.2731C>T	p.Arg911*	nonsense	0.47	somatic	Unknown

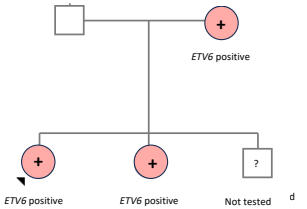
NF1	NM_001042492.2	c.574C>T	p.Arg192*	nonsense	0.41	somatic	Unknown
PTPN11	NM_002834.4	c.172A>T	p.Asn58Tyr	missense	0.19	somatic	Positive
NF1	NM_001042492.2	c.2033dup	p.Ile679Aspfs*21	frameshift	0.66	somatic	Unknown
RUNX1	NM_001754.4	NA	exon_3_5	deletion	0.5	somatic	Unknown
TP53	NM_000546.5	c.743G>A	p.Arg248Gln	missense	0.68	somatic	Negative
TP53	NM_000546.5	c.379T>C	p.Ser127Pro	missense	0.46	somatic	Negative
TP53	NM_000546.5	c.427G>A	p.Val143Met	missense	0.41	somatic	Negative
CDKN2A	NM_000077.4	c.303_304insC	p.Ala102Argfs*18	frameshift	0.49	TN	Positive

Figure Legends

Supplemental Figure 1. Pedigrees of patients diagnosed with cancer predisposition syndromes, highlighting cascade testing. Twelve family members in five pedigrees diagnosed with germline predisposition.







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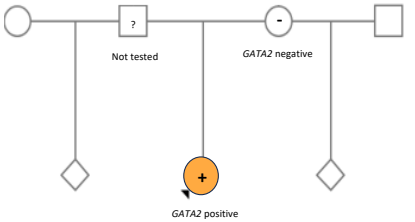

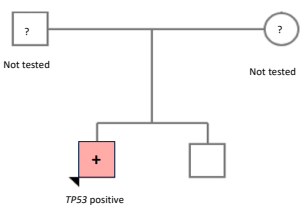

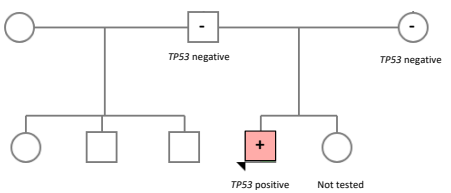

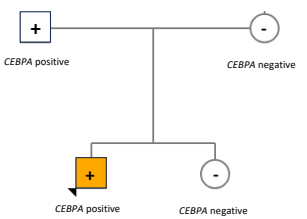

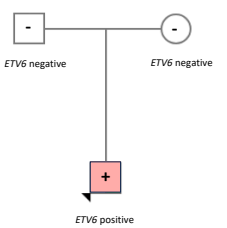

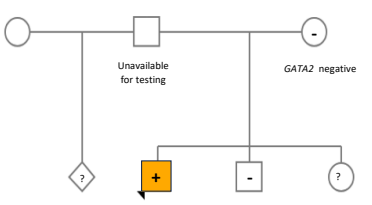

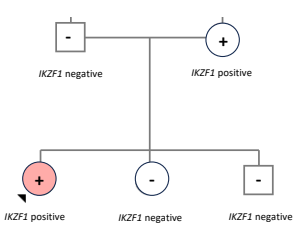

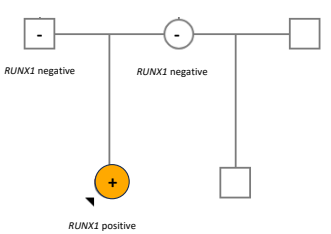

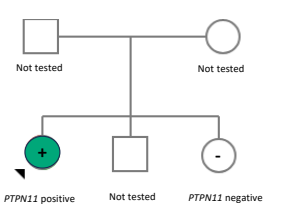
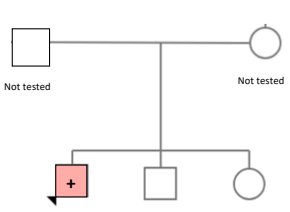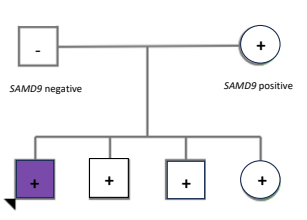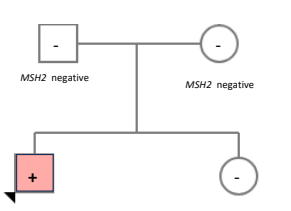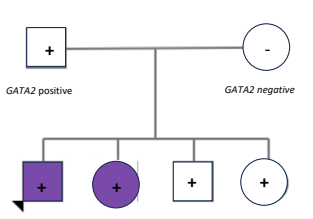
Diagnosis	
	T-ALL
	JMML
	B-ALL
	AML
	MDS
Genetic testing	
+	Positive
-	Negative
?	Recommended for testing but not yet tested