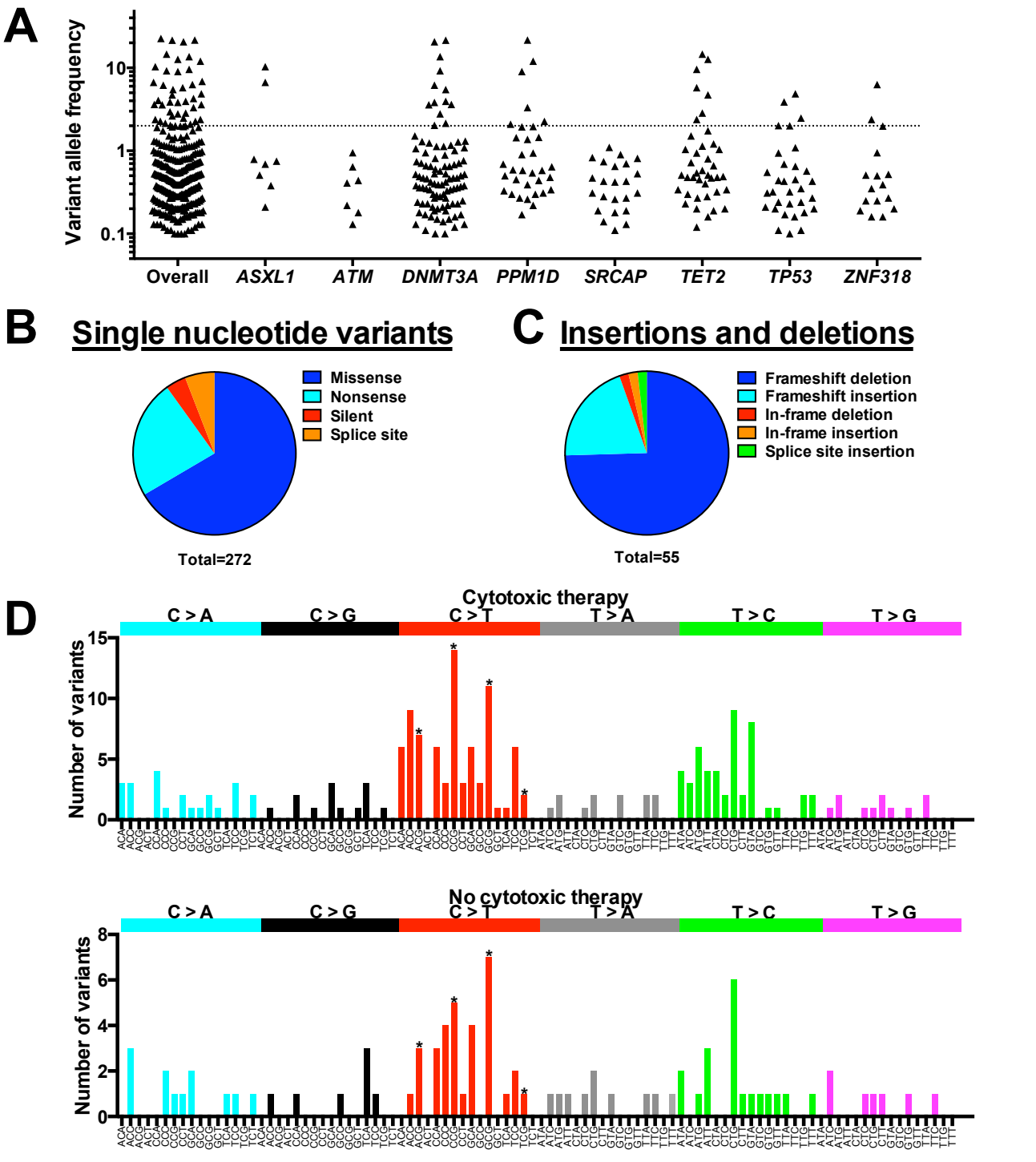
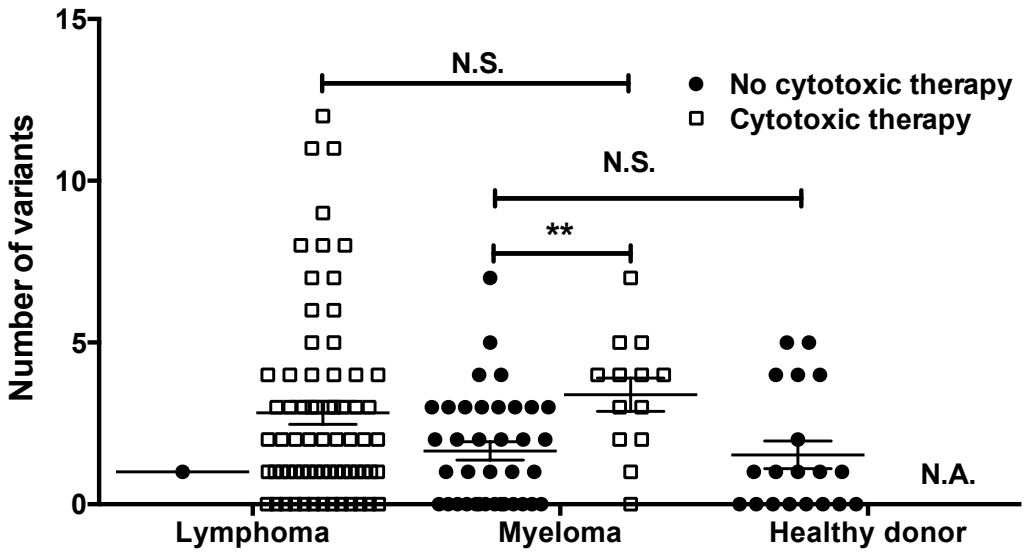
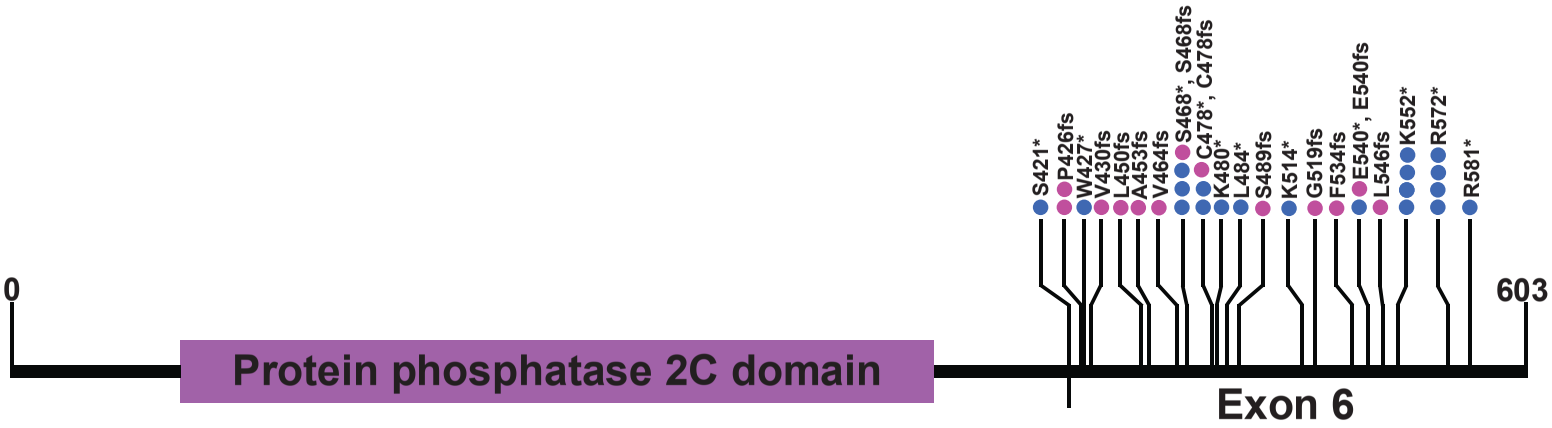


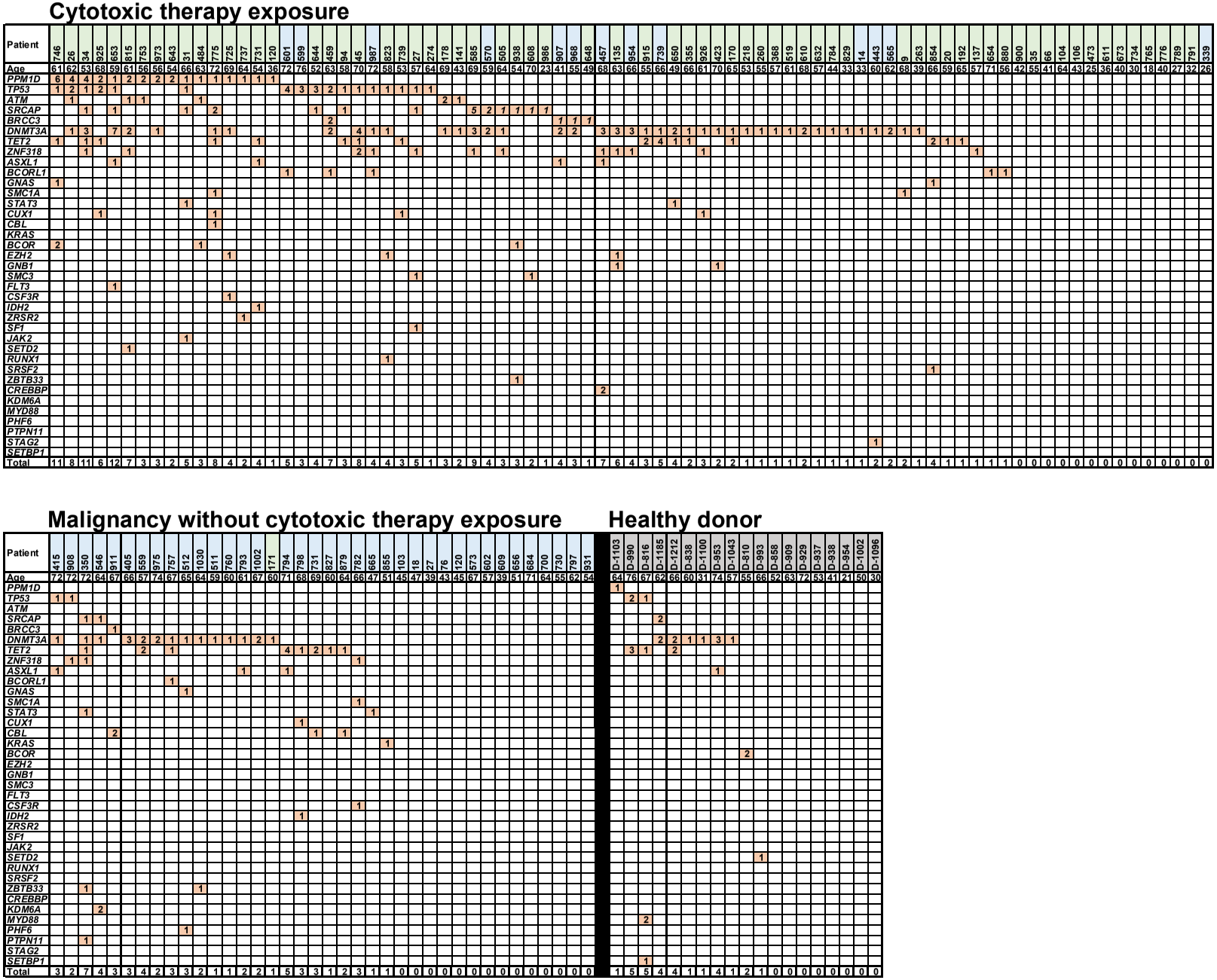
Supplementary Figure 1. Error-corrected HaloPlex sequencing allows for the detection of somatic variants at increased sensitivity. a, VAF distribution of the 327 variants identified by Haloplex error-corrected sequencing in 138 pheresis specimens and the VAF distribution of those variants in commonly mutated genes. **b,** Characterization of the 272 SNVs detected in pheresis samples by HaloPlex error-corrected sequencing. **c,** Characterization of the 55 indels detected in pheresis samples by HaloPlex error-corrected sequencing. **d,** Trinucleotide context in which the SNVs identified in pheresis samples occurred either after exposure to cytotoxic therapy (n=185) or in the absence of cytotoxic therapy exposure (n=87). * The mutation is a C to T transition mutation occurring in the context of a CpG.



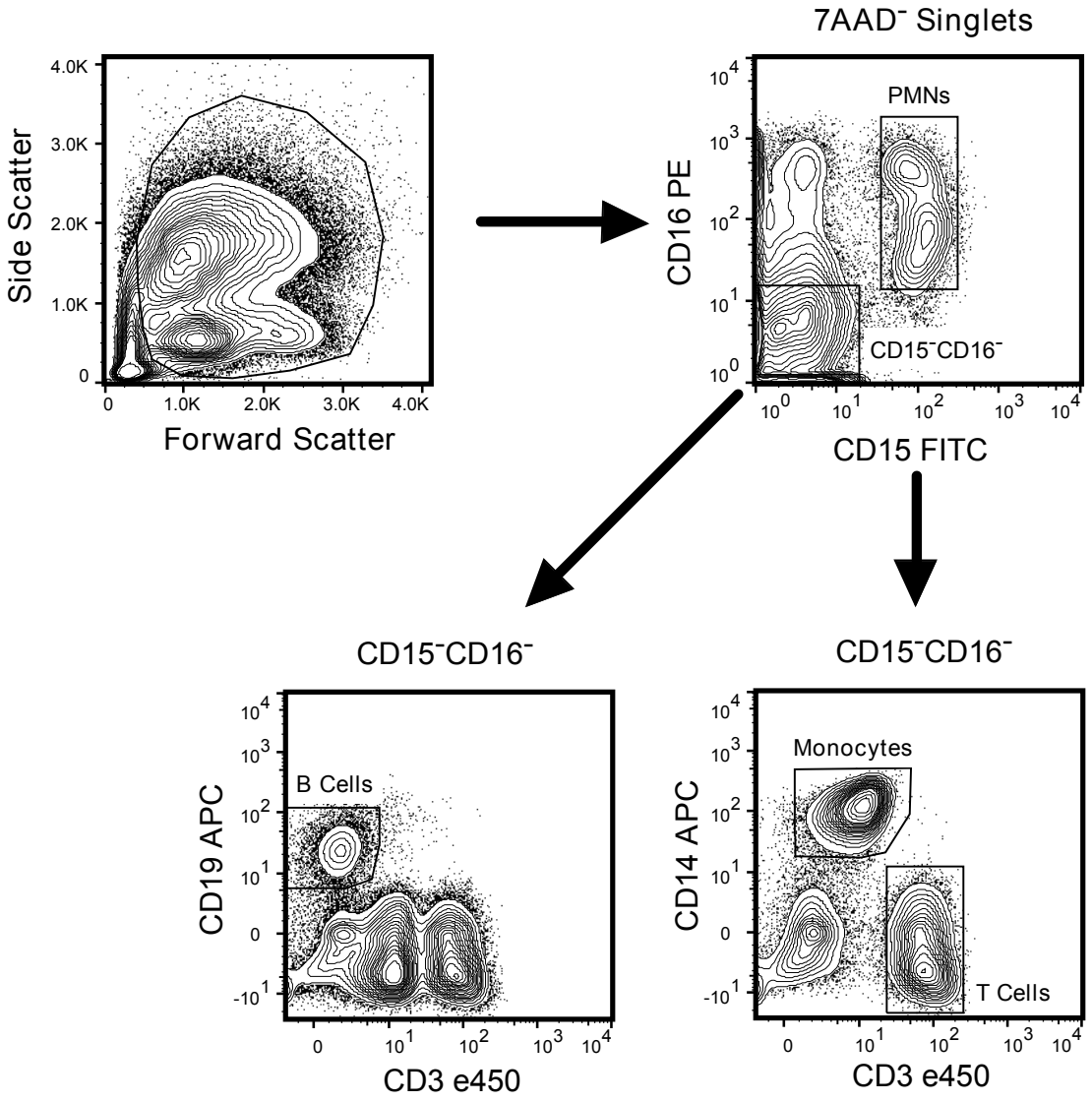
Supplementary Figure 2. Cytotoxic therapy exposure is associated with clonal hematopoiesis. The total number of clonal hematopoiesis-associated variants identified in lymphoma patients (n=69), myeloma patients (n=50), and healthy donors (n=19) grouped by whether or not these individuals previously received cytotoxic therapy. Myeloma patients receiving cytotoxic therapy (n=13) had significantly more variants identified than myeloma patients not receiving cytotoxic therapy (n=37) and were not statistically different from lymphoma patients receiving cytotoxic therapy (n=68). In contrast, myeloma patients not receiving cytotoxic therapy were not statistically different from healthy donors. N.S. Not significant. N.A. Not applicable. ** $P<0.01$. Significance was determined with a negative-binomial regression analysis. Data is represented as the mean $\pm$ the standard error of the mean.



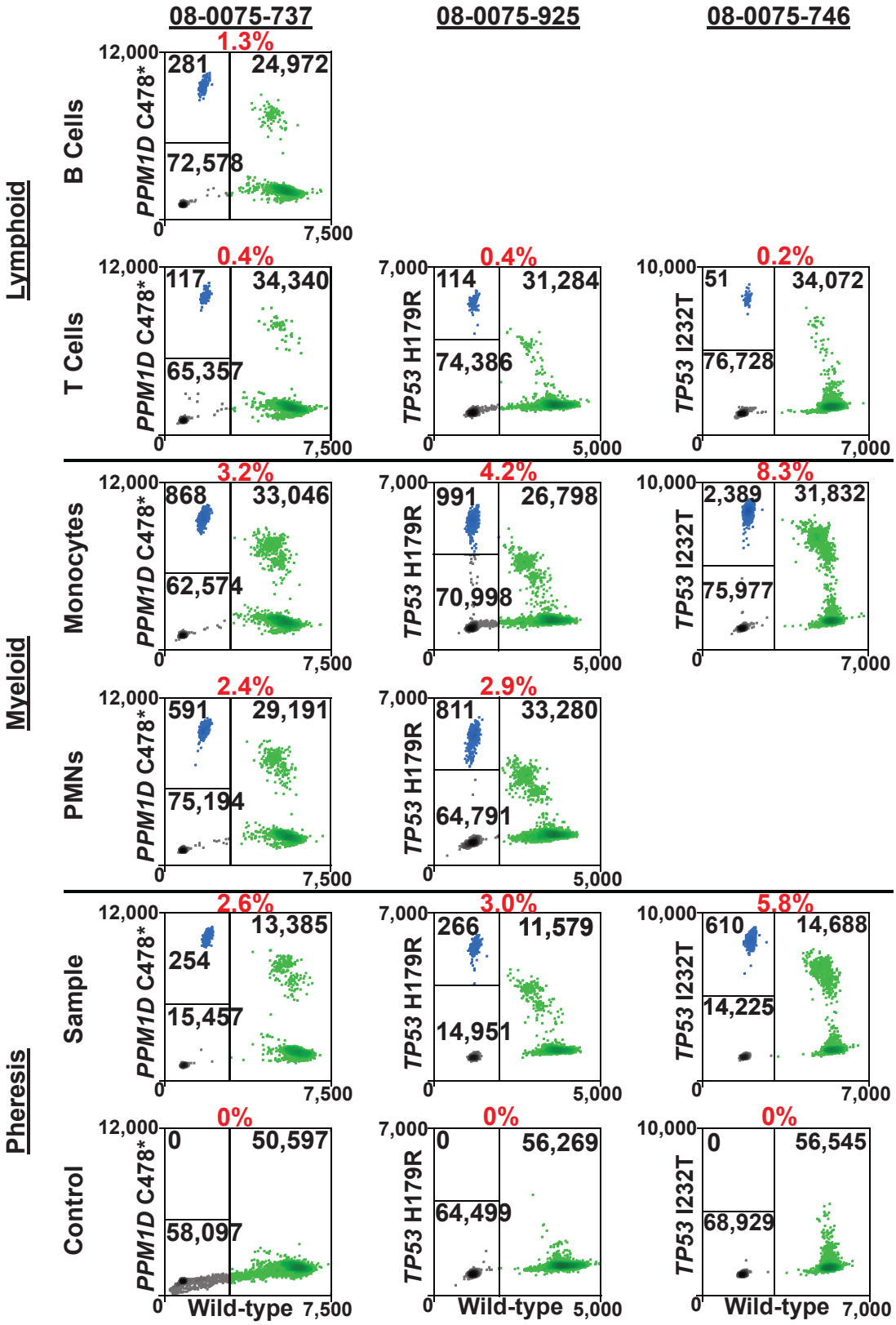
Supplementary Figure 3. Lollipop plot of *PPM1D* mutations. 33 *PPM1D* SNVs and indels were identified by HaloPlex sequencing in 138 pheresis specimens. Blue circle: nonsense mutation. Purple circle: frameshift mutation.



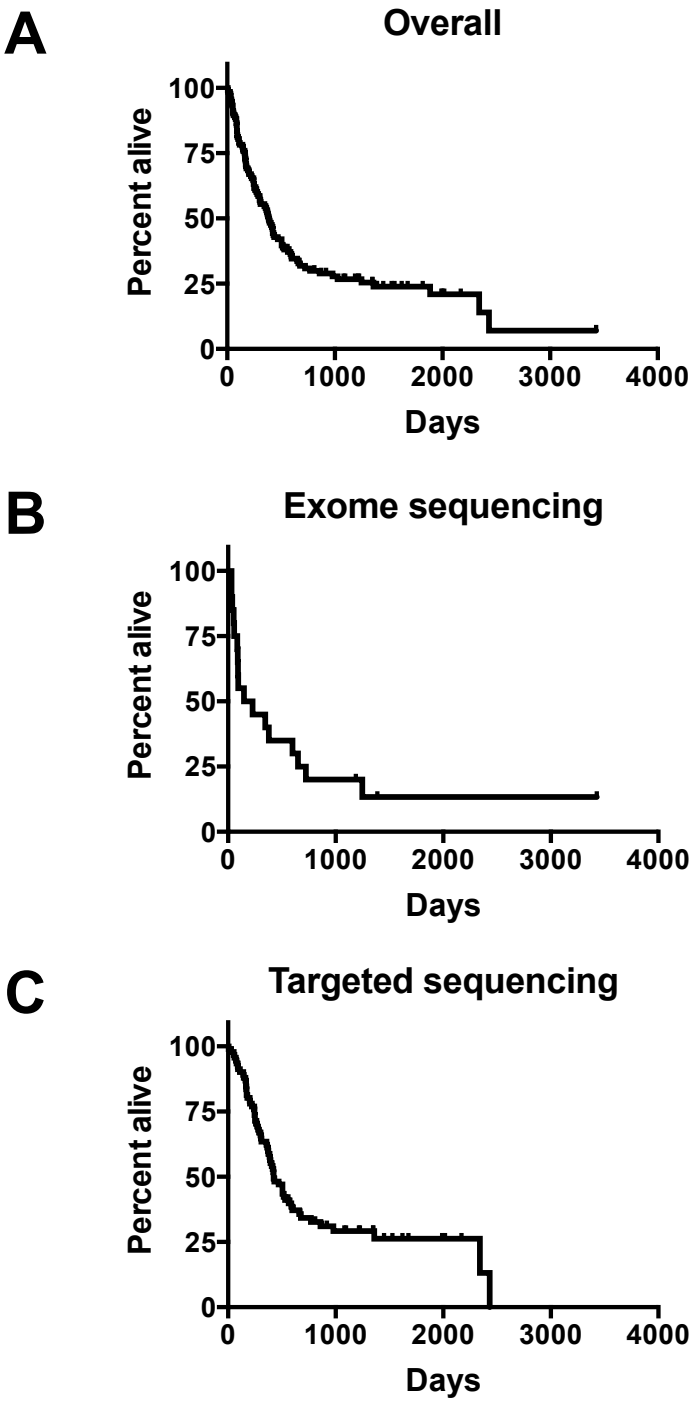
Supplementary Figure 4. Multiple variants are often present in individual patients following cytotoxic therapy. Highlighted are the gene-specific variants detected in pheresis samples with the total number of variants noted. Multiple variants are often present in individual patients after cytotoxic therapy, including multiple variants in the same gene (e.g. in *PPM1D*, *TP53*, etc.). Green: lymphoma patients. Blue: myeloma patients. Gray: healthy donors. Patients with expanded clones carrying mutations in DNA damage response genes (i.e. *PPM1D*, *TP53*, *ATM*, *SRCAP*, and *BRCC3*) are on the left.



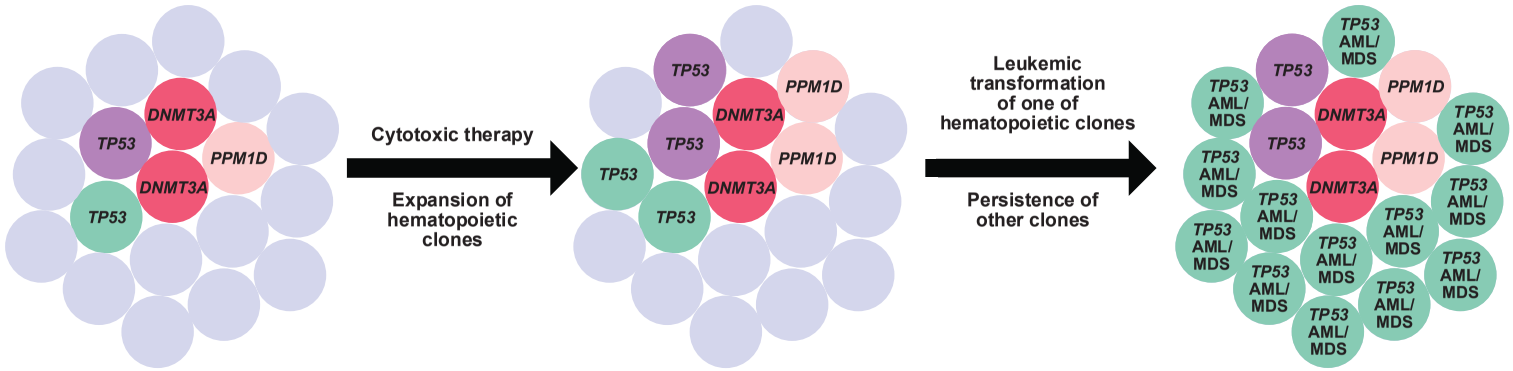
Supplementary Figure 5. Representative sorting strategy to isolate monocytes, neutrophils, B cells, and T cells. Monocytes were defined as $CD15^{-}CD16^{-}CD14^{+}$ cells. Neutrophils (PMNs) were defined as $CD15^{+}CD16^{+}$ cells. T cells were defined as $CD15^{-}CD16^{-}CD3^{+}$ cells. B cells were defined as $CD15^{-}CD16^{-}CD19^{+}$ cells. Due to most patients receiving rituximab, B cells were only able to be isolated from one patient.



Supplementary Figure 6. Representative droplet digital PCR to determine the VAFs of variants of interest in sorted cell populations. Droplets containing only the mutant allele are highlighted in blue; droplets containing the wild-type allele (with or without the mutant allele) are highlighted in green; empty droplets are gray. The number of droplets in each gate is indicated. VAFs were determined using Poisson statistics and highlighted in red. PMNs: neutrophils.



Supplementary Figure 7. Overall survival for 134 t-AML/t-MDS patients. 20 patients had exome sequencing with one published previously. 92 patients had targeted sequencing with 19 previously reported on using a different gene targeting panel. 22 patients had previously published whole genome sequencing. **a,** Overall t-AML/t-MDS cohort (n=134). **b,** Exome sequencing cohort (n=20). **c,** Targeted sequencing cohort (n=92).



Supplementary Figure 8. Model of how cytotoxic therapy shapes hematopoietic clonal evolution. Cytotoxic therapy provides a fitness advantage to multiple hematopoietic clones harboring specific mutations (e.g. in *TP53*, *PPM1D*, etc.), allowing them to expand. These clones have differing leukemogenic potential with certain clones (particularly those with mutations in *TP53*) more likely to progress to AML/MDS than others. However, non-leukemic expanded clones are often long-lived and may co-exist with the malignant clone at diagnosis.

Supplementary Table 1 Detailed clinical data for myeloma patients assessed with error-corrected sequencing

Patient (UPN)	Gender	Age	Myeloma treatment prior to pheresis collection	Radiation? (Yes/No)	Cytotoxic therapy? (Yes/No)	Time from initial treatment to transplant (months)	Conditioning regimen
14	M	33	Thalidomide/dexamethasone x 6	Yes	Yes	6	Melphalan
18	F	47	Thalidomide/dexamethasone	No	No	27	Melphalan
27	F	39	Thalidomide/dexamethasone	No	No	5	Melphalan
76	M	43	Thalidomide/dexamethasone x 7 months; lenalidamide/dexamethasone x 2	No	No	16	Melphalan
103	M	45	Thalidomide/dexamethasone; lenalidamide/dexamethasone	No	No	14	Melphalan
120	F	45	Thalidomide/dexamethasone	No	No	5	Melphalan
339	M	26	VRD x 4	Yes	Yes	27	Melphalan
350	F	72	VRD x 3	No	No	4	Melphalan
405	F	66	VD x 3	No	No	4	Melphalan
415	M	72	VRD x 3	No	No	4	Melphalan
443	M	60	Doxil/dexamethasone/bortezomib x 3	No	Yes	5	Melphalan
457	M	68	RD; VRD	Yes	Yes	N.A.	N.A.
511	M	59	Thalidomide/dexamethasone	No	No	26	Melphalan
512	F	65	KRd x 5	No	No	unknown	Melphalan
546	F	64	VD x 4	No	No	5	Melphalan
559	F	57	VRD x 4	No	No	6	Melphalan
565	F	62	VD x 1; VRD x 3	Yes	Yes	3	Melphalan
570	F	59	VD x 8	Yes	Yes	19	Melphalan
573	M	67	VRD x 3	No	No	4	Melphalan
599	M	76	VD x 7; RD x 4; VD x 4; DVD x 2	Yes	Yes	21	Melphalan
601	F	72	RD x 7	Yes	Yes	unknown	Melphalan
602	F	57	VRD x 4	No	No	4	Melphalan
609	M	39	VRD x 4	No	No	5	Melphalan
656	M	51	VRD x 4	No	No	5	Melphalan
665	F	47	VD x 4; lenalidamide x 3	No	No	4	Melphalan
684	F	71	RD; VRD x 3; cyclophosphamide mobilization	No	No	12	Melphalan
700	M	64	VD x 1; VRD < 1; VD x 3	No	No	6	Melphalan
730	M	55	VD x 4	No	No	3	Melphalan
731	M	69	VRD x 3	No	No	4	Melphalan
739	M	66	VRD x 3	Yes	Yes	5	Melphalan
757	M	67	VD x 5	No	No	unknown	Melphalan
760	F	60	VRD x 4	No	No	5	Melphalan
782	M	66	VRD x 3	No	No	4	Melphalan
793	M	61	VRD x 3	No	No	3	Melphalan
794	M	71	VRD x 3	No	No	4	Melphalan
797	F	62	VD x 1; VRD x 4	No	No	5	Melphalan
798	M	68	VRD x 4	No	No	7	Melphalan
827	M	60	VD x 4	No	No	5	Melphalan
855	M	51	VRD x 4	No	No	4	Melphalan
879	M	64	KRd x 4	No	No	4	Melphalan
907	M	41	KRd x 4	Yes	Yes	6	Melphalan
908	M	72	VRD x 4	No	No	5	Melphalan
911	F	67	VRD x 4	No	No	4	Melphalan
931	M	54	KRd x 3	No	No	4	Melphalan
954	F	66	VD x 1; VRD x 3	Yes	Yes	5	Melphalan
968	M	55	VRD x 4	Yes	Yes	4	Melphalan
975	F	74	VRD x 3; RD x 1	No	No	8	Melphalan
987	M	72	VD x 2; VRD x 5	Yes	Yes	6	Melphalan
1002	M	67	VRD x 4	No	No	4	Melphalan
1030	F	64	VD x 6	No	No	9	Melphalan

N.A.: not applicable; UPN: unidentified patient number
Treatment regimens are as follows:
DVD: doxil, vincristine, dexamethasone
KRd: carfilzomib, lenalidamide, dexamethasone
RD: lenalidamide, dexamethasone
VD: bortezomib, dexamethasone
VRD: bortezomib, lenalidamide, dexamethasone

Supplementary Table 2 Genes targeted by error-corrected sequencing

ASXL1	*EZH2*	*NRAS*	*SRCAP*
ATM	*FLT3*	*PHF6*	*SRSF2*
ATRX	*GNAS*	*PPM1D*	*STAG2*
BCOR	*GNB1*	*PTPN11*	*STAT3*
BCORL1	*IDH1*	*RAD21*	*TET2*
BRCC3	*IDH2*	*RUNX1*	*TP53*
CBL	*JAK2*	*SETBP1*	*U2AF1*
CEBPA	*KDM6A*	*SETD2*	*ZBTB33*
CREBBP	*KRAS*	*SF1*	*ZNF318*
CSF3R	*LUC7L2*	*SF3B1*	*ZRSR2*
CUX1	*MYD88*	*SMC1A*	
DNMT3A	*NPM1*	*SMC3*	

Supplementary Table 3 Association between patient clinical features and hematopoietic clonal expansion

	Age		Radiation therapy		Radiation therapy (age-adjusted)		Chemotherapy		Chemotherapy (age-adjusted)		Cytoreductive therapy		Cytoreductive therapy (age-adjusted)	
	IRR	**P Value**	**IRR**	**P Value**	**IRR**	**P Value**	**IRR**	**P Value**	**IRR**	**P Value**	**IRR**	**P Value**	**IRR**	**P Value**
Number of mutations	1.05	< 0.001	1.10	0.70	1.18	0.45	1.51	0.03	1.85	< 0.001	1.84	0.001	2.28	< 0.001
Presence of:	**OR**	**P Value**	**OR**	**P Value**	**OR**	**P Value**	**OR**	**P Value**	**OR**	**P Value**	**OR**	**P Value**	**OR**	**P Value**
Any Mutation	1.10	< 0.001	2.19	0.25	3.98	0.07	2.23	0.06	4.87	0.003	2.98	0.009	9.21	< 0.001
DNMT3A	1.04	0.003	1.95	0.19	2.20	0.13	1.13	0.85	1.32	0.54	1.89	0.10	2.34	0.03
PPM1D	1.03	0.26	0.91	1.00	0.95	1.00	19.54	<0.001	22.80	< 0.001	13.61	0.002	15.45	< 0.001
TP53	1.09	< 0.001	1.93	0.35	2.17	0.29	2.80	0.07	4.13	0.01	3.49	0.04	4.94	0.009
SRCAP	1.02	0.32	0.26	0.30	0.27	0.32	3.28	0.07	3.63	0.05	3.41	0.09	3.76	0.06
TET2	1.08	< 0.001	0.29	0.14	0.28	0.15	1.27	0.73	1.65	0.37	1.03	1.00	1.28	0.76
ZNF318	1.09	0.004	1.09	1.00	1.14	1.00	1.52	0.63	2.04	0.33	3.11	0.13	4.21	0.05
ATM	1.02	0.69	0.86	1.00	0.89	1.00	8.47	0.03	9.05	0.03	6.07	0.08	6.50	0.06

IRR: Incident rate ratio; OR: exact odds ratio

Supplementary Table 4 Gene panel for targeted t-AML/t-MDS sequencing

ABCG2	*CMYA5*	*FAM40B*	*IKZF4*	*MLL3*	***PPM1D***	*ST13P13*
ABTB1	*CNTN5*	*FAM47A*	*ILDR1*	*MROH5*	*PPP1R3A*	***STAG2***
ADAM11	*CNTNAP4*	*FAM57B*	*ITPR3*	*MTA2*	*PRAMEF2*	***STAT3***
ADCY5	*COL12A1*	*FAM5C*	*JAK1*	*MTMR8*	*PRPF4B*	*STC2*
AKAP13	*COL5A3*	*FAM65A*	***JAK2***	*MTUS2*	*PRPF8*	*STRN*
ALPK3	***CREBBP***	*FAM70B*	*JAK3*	*MUC16*	*PSME4*	*SUZ12*
ANK2	*CRISPLD1*	*FCGBP*	*KCNA4*	*MUC5B*	*PTCH1*	*SYNGAP1*
APOB	*CROCC*	*FKBP8*	*KCNH2*	*MYC*	***PTPN11***	*SYT15*
ARAP2	*CSMD1*	*FLG*	*KCNK13*	*MYH4*	*PTPRN*	*TCEAL3*
ASXL1	*CSMD3*	*FLRT2*	*KCNQ2*	*MYO5B*	*PTPRT*	*TCEAL6*
ATG16L1	*CUEDC1*	*FLT1*	*KCNT1*	*MYOC*	***RAD21***	*TET1*
ATM	*CUL1*	***FLT3***	*KCNU1*	*MYOM3*	*RBBP4*	***TET2***
ATP10B	*DCHS2*	*FOXP1*	*KDM3B*	*NALCN*	*RFC3*	*THRAP3*
ATP2B3	*DCLK1*	*FREM2*	***KDM6A***	*NAV1*	*RIMS1*	*TMEM104*
BCOR	*DDR2*	*FRYL*	*KDR*	*NF1*	*RNF213*	*TNC*
BCORL1	*DDX11*	*GALNTL4*	*KIAA0240*	*NLRC4*	***RUNX1***	*TOP3B*
BMPER	*DDX41*	*GAS6*	*KIAA1267*	*NMUR2*	*RUNX1T1*	***TP53***
BOD1L	*DIS3*	*GATA2*	*KIAA1529*	***NPM1***	*RYR1*	*TRA2B*
BRCC3	*DLC1*	*GBP4*	*KIAA1683*	*NR2E1*	*RYR3*	*TRPM3*
BSN	*DNAH5*	*GIGYF2*	*KIF2B*	***NRAS***	*SBF1P1*	*TTBK1*
C10orf118	*DNAH9*	*GJB3*	*KIT*	*NRXN3*	*SCAF8*	*TUBA3C*
C10orf28	*DNAI1*	***GNAS***	***KRAS***	*NTRK3*	*SCARB1*	*TYK2*
C17orf97	***DNMT3A***	***GNB1***	*KRT19*	*OR11H12*	*SCML2*	***U2AF1***
C5	*DNMT3B*	*GPR112*	*KRT79*	*OR13H1*	*SCN1A*	*UNC5B*
CACNA1B	*DOCK2*	*GPR183*	*KSR2*	*OR8B12*	*SEMA3A*	*USP9X*
CACNA1E	*DRD2*	*GRID1*	*LNX1*	*P2RY2*	*SEMA4A*	*VARS2*
CACNA1G	*DSCAM*	*GRIK2*	*LOC100129218*	*PCDHA13*	***SETBP1***	*VCAN*
CACNA2D3	*DST*	*GRIK4*	*LOC100132800*	*PCDHA6*	***SF3B1***	*WAC*
CADM2	*DYNC2H1*	*GRM3*	*LOC730032*	*PCDHB1*	*SHC1*	*WT1*
CADPS	*DYSF*	*GRM8*	*LRBA*	*PCDHB18*	*SHROOM2*	*XIRP1*
CALR	*E2F8*	*GSTK1*	*LRIT1*	*PDCD2L*	*SI*	***ZBTB33***
CBFB	*EDIL3*	*HECW1*	*LRP1B*	*PHACTR1*	*SLC12A3*	*ZC3H18*
CBL	*EED*	*HIVEP1*	*LRRC4*	***PHF6***	*SLC39A5*	***ZNF318***
CCDC67	*EEF1A1P29*	*HMCN1*	*MAGI2*	*PHIP*	***SMC1A***	*ZNF687*
CD74	*EGFR*	*HNRNPK*	*MAP1B*	*PKD1L2*	***SMC3***	
CEBPA	*EPHA10*	*HSP90B3P*	*MAP2*	*PKD2L1*	*SMG1*	
CECR2	*EPPK1*	*HYDIN*	*MED12*	*PKHD1*	*SPEG*	
CELSR3	*ETV6*	***IDH1***	*MEFV*	*PKHD1L1*	*SPEN*	
CHD4	***EZH2***	***IDH2***	*MEGF8*	*PLCE1*	***SRCAP***	
CLEC18B	*FAM154B*	*IGHG3*	*MIR142*	*PLEKHH1*	***SRSF2***	

HaloPlex genes highlighted. HaloPlex genes not included in the t-AML/t-MDS targeted list: *ATRX*, *CSF3R*, *CUX1*, *LUC7L2*, *MYD88*, *SETD2*, *SF1*, and *ZRSR2*.