

Supplemental Information 1: the OGM settings.

Data-analysis for the *de novo* assembly and rare variant analysis (RVA) was optimized by comparing several filter settings (Supplemental Table 1). Settings with a variable number of aberrations are the positive predictive value (PPV) of the intra-fusions, the PPV of the inter-translocations, the presence of the variants in the control group and the masking of CNV-sensitive regions of the genome (Supplemental Table 2 and 3). As hematologic malignancies arise at all ages (Prog Tumor Res. 2016;43:87-100, Juliusson et. al.), we used the least stringent filtering of the aberrations in the control group. Some aberrations were filtered when masking the CNV-enriched regions or selecting the genes of interest using the Access software. For example, an inversion (3q25.33;q26.2) that includes *MECOM* was filtered out due to a bug in the Access v.1.7 software. Further, translocations and fusions without a gene of interest were filtered out even though these aberrations can be of clinical significance. As a consequence, we decided to use settings D (Supplemental Table 1) which had the lowest specificity and highest sensitivity for the final analysis. Inverted aberrations in the genes of interest and disease-causing aberrations without a gene of interest were filtered using a disease-specific BED-file (Supplemental Information 2). For this reason, disease-specific BED files were used to visualize the regions of interest, but not for initial filtering.

The final settings (settings D) are: insertion recommended (confidence 0) and minimum size 500 bp, deletion recommended (confidence 0) and minimum size 500 bp, inversion recommended (confidence 0.7) and minimum size 30 kbp, duplication recommended (confidence -1) and minimum size 30 kbp, intra-fusion recommended (confidence 0.05), and; inter-translocation recommended (confidence 0.05). Detected events were subsequently filtered (less than or equal to 1%) using a database of approximately 300 individuals from 33 different ethnicities with no known genetic disorder available in Access v.1.7. Settings

applied to all SV types were: SV-masking = all structural variants, VAF filter min = 0, VAF filter max = 1, SV self-molecule check = SV found in self-molecules, self-molecule count = 5, SV overlapping genes filter = all SVs. CNV filters were: CNV type = all, copy CNV confidence = recommended (0.99), CNV minimum size = 500 kbp, CNV masking filter = all. Aneuploidy filters were: aneuploidy type = all, aneuploidy confidence = recommended (0.95). AOH/LOH filters (*de-novo*) were: AOH/LOH minimum size = 0bp. GRCh37 hg19 (UCSC, Santa Cruz USA (UCSC)) was used as a reference genome.

Supplemental Table 1: Filter settings tested.

	Filterset A	Filterset B	Filterset C	Filterset D	Filterset E
Insertion	0	0	0	0	0
Deletion	0	0	0	0	0
Inversion	0.7	0.7	0.7	0.7	0.7
Duplication	-1	-1	-1	-1	-1
Intra-fusion	0.05	0.3*	0.05	0.05	0.3*
Inter-translocation	0.05	0.65*	0.05	0.05	0.65*
Control-group	0%	0%	1%	1%	1%
SV masking	all	all	all	all	all
Self-molecules count	5	5	5	5	5
SV chimeric score	show not failing	show not failing	show not failing	show not failing	show not failing
Copy Number Variants	0.99	0.99	0.99	0.99	0.99
Copy Number Variants masking	non-masked only	non-masked only	non-masked only	all	all
Aneuploidy	0.95	0.95	0.95	0.95	0.95

The settings of the several filters are shown in this table. The following positive predictive values are recommended in Bionano Access v.1.7: insertion/deletion = 0, inversion = 0.7, duplications = -1, intra-fusion = 0.05, inter-translocation = 0.05, CNV = 0.99, aneuploidy = 0.95. Recommended Bionano Access v.1.6 settings are the same except: intra-fusion = 0.3 and inter-translocation = 0.65. A control database was used for filtering. Variants with an occurrence of 0 or 1% in the database were considered for analysis. CNV-sensitive regions were masked with filter settings A, B and C. Other settings that were applied to all were: SV-masking = all, self-molecules-counts = 5, SC-chimeric-score-show-not-failing.

Supplemental Table 2: number of aberrations with the several filter-sets, *de-novo* pipeline

Type of aberration	Number of aberrations (Mean/SD)		Filterset A (Mean/SD)		Filterset B (Mean/SD)		Filterset C (Mean/SD)		Filterset D (Mean/SD)		Filterset E (Mean/SD)	
Insertion	7090.4	2588.4	8.3	2.9	8.3	2.9	15.2	4.3	15.2	4.3	15.2	4.3
Deletion	3538.3	1547.2	12.9	3.7	12.9	3.7	25.1	4.4	25.1	4.4	25.1	4.4
Inversion	207.2	24.1	0.2	0.5	0.2	0.5	0.4	0.7	0.4	0.7	0.4	0.7
Duplication	119.4	53.1	2.2	1.7	2.2	1.7	2.9	2.3	2.9	2.3	2.9	2.3
Intra-Fusion	99.0	57.0	4.7	5.7	1.0	1.2	5.7	5.7	5.7	5.7	1.2	1.4
Inter-Translocation	61.6	17.6	0.8	1.3	0.6	1.3	1.1	1.5	1.1	1.5	0.7	1.3
AOH/LOH	10.1	3.0	10.1	3.0	10.1	3.0	10.1	3.0	10.1	3.0	10.1	3.0
CNV gain	28.6	9.7	2.2	2.6	2.2	2.6	2.2	2.6	2.6	2.7	2.6	2.7
CNV loss	31.7	3.9	1.1	1.9	1.1	1.9	1.1	1.9	1.2	1.9	1.2	1.9
aneuploidy Gain	0.1	0.3	0.1	0.3	0.1	0.3	0.1	0.3	0.1	0.3	0.1	0.3
aneuploidy Loss	0.1	0.3	0.06	0.2	0.06	0.2	0.06	0.2	0.06	0.2	0.06	0.2

In the first column, the number of aberrations (mean, SD) after *de-novo* assembly are shown without filtering. In the other columns, the number of aberrations (mean, SD) are depicted for each filter set. The different settings are presented in table 1.

Supplemental Table 3: number of aberrations with the several filter-sets, RVA

Type of aberration	Number of aberrations (Mean/SD)		Filterset A (Mean/SD)		Filterset B (Mean/SD)		Filterset C (Mean/SD)		Filterset D (Mean/SD)		Filterset E (Mean/SD)	
Insertion	771.2	64.0	6.6	3.3	6.6	3.3	10.4	2.9	10.4	2.9	10.4	2.9
Deletion	751.5	34.2	14.1	5.3	14.1	5.3	21.4	5.4	21.4	5.4	21.4	5.4
Inversion	198.5	38.8	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
Duplication	237.0	99.8	2.1	1.1	2.1	1.1	3.6	1.8	3.6	1.8	3.6	1.8
Intra-Fusion	108.2	50.3	2.6	1.2	0.6	0.8	3.9	1.8	3.9	1.8	0.6	0.8
Inter-Translocation	58.9	27.7	0.5	1.4	0.1	0.3	0.6	1.4	0.6	1.4	0.1	0.3
CNV gain	25.3	8.5	1.5	1.8	1.5	1.8	1.5	1.8	1.6	2.1	1.6	2.1
CNV loss	37.8	12.6	1.1	2.3	1.1	2.3	1.1	2.3	1.1	2.3	1.1	2.3
aneuploidy Gain	0.2	0.4	0.2	0.4	0.2	0.4	0.2	0.4	0.2	0.4	0.2	0.4
aneuploidy Loss	0.2	0.4	0.1	0.3	0.1	0.3	0.1	0.3	0.1	0.3	0.1	0.3

In the first column, the number of aberrations (mean, SD) after rare variant analysis are shown without filtering.

In the other columns, the number of aberrations (mean, SD) are depicted for each filter set. The different settings are presented in table 1.

Supplemental Information 2: BED files

Myeloid BED file

Myeloid BED file GRCh37 (hg19)			
<i>Gene</i>	<i>Chr</i>	<i>Chr Start</i>	<i>Chr End</i>
<i>PRDM16</i>	1	2985741	3355185
<i>CSF3R</i>	1	36931643	36948915
<i>MPL</i>	1	43803474	43820135
<i>RBM15</i>	1	110881944	110889303
<i>NRAS</i>	1	115247084	115259515
<i>DNMT3A</i>	2	25455829	25565459
<i>SF3B1</i>	2	198256697	198299771
<i>IDH1</i>	2	209100952	209119806
<i>RASSF1</i>	3	50367216	50378367
<i>GATA2</i>	3	128198264	128212030
<i>MECOM</i>	3	168801286	169381563
<i>FIP1L1</i>	4	54243819	54326103
<i>CHIC2</i>	4	54875957	54930815
<i>PDGFRA</i>	4	55095263	55164412
<i>KIT</i>	4	55524094	55606881
<i>TET2</i>	4	106067841	106200960
<i>PDGFRB</i>	5	149493401	149535422
<i>RPS14</i>	5	149823791	149829319
<i>RANBP17</i>	5	170288895	170727019
<i>NPM1</i>	5	170814707	170837888
<i>DEK</i>	6	18224399	18264799
<i>CUX1</i>	7	101459183	101927250
<i>EZH2</i>	7	148504463	148581441
<i>MNX1</i>	7	156786744	156802129
<i>MNX1</i>	7	156797546	156803347
<i>PCM1</i>	8	17780365	17887457
<i>FGFR1</i>	8	38268655	38326352
<i>KAT6A</i>	8	41786996	41909505
<i>RUNX1T1</i>	8	92967194	93115454
<i>JAK2</i>	9	4985244	5128183
<i>MLLT3</i>	9	20341662	20622514
<i>ABL1</i>	9	133589267	133763062
<i>NUP214</i>	9	134000980	134110057
<i>MLLT10</i>	10	21823573	22032559
<i>HRAS</i>	11	532241	535550
<i>NUP98</i>	11	3696239	3819022
<i>WT1</i>	11	32409321	32457081
<i>CCND1</i>	11	69455872	69469242
<i>PICALM</i>	11	85668213	85780139
<i>ZBTB16</i>	11	113931287	114121397
<i>KMT2A</i>	11	118307204	118397539

<i>CBL</i>	11	119076985	119178859
<i>ETV6</i>	12	11802787	12048325
<i>ETNK1</i>	12	22778075	22843608
<i>KRAS</i>	12	25357722	25403854
<i>PTPN11</i>	12	112856535	112947717
<i>NCOR2</i>	12	124808956	125052010
<i>FLT3</i>	13	28577410	28674729
<i>RB1</i>	13	48877882	49056026
<i>PML</i>	15	74287013	74340155
<i>IDH2</i>	15	90627211	90645708
<i>CREBBP</i>	16	3775055	3930121
<i>MYH11</i>	16	15796991	15950887
<i>FUS</i>	16	31191430	31206192
<i>CBFB</i>	16	67063049	67134958
<i>PRPF8</i>	17	1553922	1588176
<i>TP53</i>	17	7571719	7590868
<i>NF1</i>	17	29421944	29704695
<i>RARA</i>	17	38465422	38513895
<i>SRSF2</i>	17	74730196	74733493
<i>SETBP1</i>	18	42260137	42648475
<i>CALR</i>	19	13049413	13055304
<i>CEBPA</i>	19	33790839	33793470
<i>ASXL1</i>	20	30946146	31027122
<i>RUNX1</i>	21	36160097	36421595
<i>ERG</i>	21	39739182	40033704
<i>U2AF1</i>	21	44513065	44527688
<i>BCR</i>	22	23522551	23660224
<i>MKL1</i>	22	40806291	41032690
<i>ZRSR2</i>	23	15808573	15841382
<i>BCOR</i>	23	39910498	40036582
<i>STAG2</i>	23	123094409	123236505

Mature B cell neoplasm BED file

Mature B cell neoplasm BED file GRCh37 (hg19)			
<i>Gene</i>	Chr	Chr Start	Chr End
<i>FAF1</i>	1	50906935	51425936
<i>CDKN2C</i>	1	51434366	51440309
<i>BCL10</i>	1	85731459	85742587
<i>MTF2</i>	1	93544792	93604638
<i>TMED5</i>	1	93615299	93646246
<i>FAM46C</i>	1	118148604	118171011
<i>CKS1B</i>	1	154947118	154951725
<i>ACP1</i>	2	264868	278282
<i>MYCN</i>	2	16080559	16087129
<i>ALK</i>	2	29415639	30144477

<i>MSH2</i>	2	47630205	47710367
<i>BCL11A</i>	2	60684328	60780633
<i>REL</i>	2	61108629	61155291
<i>XPO1</i>	2	61705068	61765418
<i>CXCR4</i>	2	136871918	136875725
<i>SF3B1</i>	2	198256697	198299771
<i>MYD88</i>	3	38179969	38184510
<i>SETD2</i>	3	47057897	47205467
<i>CDC25A</i>	3	48198667	48229801
<i>ATRIP</i>	3	48488113	48507708
<i>FOXP1</i>	3	71003864	71633140
<i>PIK3A-PIK3CA</i>	3	178866310	178952497
<i>BCL6</i>	3	187439164	187463513
<i>TP63</i>	3	189349215	189615068
<i>FGFR3</i>	4	1795039	1810599
<i>WHSC1</i>	4	1873123	1983934
<i>NPM1</i>	5	170814707	170837888
<i>DUSP22</i>	6	292056	351355
<i>IRF4</i>	6	391738	411443
<i>CCND3</i>	6	41902671	42016610
<i>SEC63</i>	6	108188959	108279482
<i>FOXO3</i>	6	108881025	109005971
<i>MYB</i>	6	135502452	135540311
<i>POT1</i>	7	124462439	124570037
<i>BRAF</i>	7	140433812	140624564
<i>TRAIL- TNFRSF10A</i>	8	23048969	23082680
<i>TRIM35</i>	8	27142403	27168834
<i>MYC</i>	8	128748314	128753680
<i>PVT1</i>	8	128806778	129113499
<i>MAFA</i>	8	144510229	144512602
<i>NOTCH1</i>	9	139388884	139440238
<i>PTEN</i>	10	89623194	89731687
<i>PIK3A</i>	10	98353068	98480279
<i>CCND1</i>	11	69455872	69469242
<i>MRE11A</i>	11	94150468	94227040
<i>BIRC3</i>	11	102188180	102210135
<i>ATM</i>	11	108093558	108239826
<i>H2AFX</i>	11	118964584	118966177
<i>CCND2</i>	12	4382901	4414522
<i>RB1</i>	13	48877882	49056026
<i>DLEUregion</i>	13	50456688	51417885
<i>DLEU2</i>	13	50556687	50699677
<i>BCMS-DLEU</i>	13	50975361	51205735
<i>TGDS</i>	13	95226307	95248529
<i>MGA</i>	15	41952609	42062141
<i>IGH</i>	16	31973408	31973499
<i>MAF</i>	16	79627744	79634622

<i>PLCG2</i>	16	81812898	81991899
<i>TP53</i>	17	7571719	7590868
<i>CLTC</i>	17	57697049	57774317
<i>MALT1</i>	18	56338617	56417371
<i>BCL2</i>	18	60790578	60986613
<i>MAFB</i>	20	39314516	39317876
<i>PRAME</i>	22	22890117	22901768
<i>BTK</i>	23	100604434	100641212

ALL BED file

ALL BED file GRCh37 (hg19)			
<i>Gene</i>	Chr	Chr Start	Chr End
<i>TAL1</i>	1	47681961	47698007
<i>STIL</i>	1	47715810	47779819
<i>JAK1</i>	1	65298905	65432187
<i>MEF2D</i>	1	156433512	156460391
<i>PBX1</i>	1	164528596	164821060
<i>ABL2</i>	1	179068461	179112224
<i>FHIT</i>	3	59735035	61237133
<i>PDGFRA</i>	4	55095263	55164412
<i>AFF1</i>	4	87856153	88062206
<i>DUX4</i>	4	190998875	191000255
<i>IL3</i>	5	131396346	131398896
<i>CSF1R</i>	5	149432853	149492935
<i>PDGFRB</i>	5	149493401	149535422
<i>EBF1</i>	5	158122922	158526788
<i>TLX3</i>	5	170736287	170739138
<i>RUNX2</i>	6	45296053	45518819
<i>MYB</i>	6	135502452	135540311
<i>MLLT4-AS1</i>	6	168224569	168227476
<i>MLLT4</i>	6	168227670	168372700
<i>HOXA13</i>	7	27236498	27239725
<i>IKZF1</i>	7	50344377	50472798
<i>TRB</i>	7	142197571	142198055
<i>MYC</i>	8	128748314	128753680
<i>JAK2</i>	9	4985244	5128183
<i>MLLT3</i>	9	20344967	20622514
<i>CDKN2A</i>	9	21967750	21994490
<i>CDKN2B</i>	9	22002901	22009312
<i>PAX5</i>	9	36833271	37034476
<i>ABL1</i>	9	133589267	133763062
<i>NUP214</i>	9	134000980	134109091
<i>MLLT10</i>	10	21823573	22032559
<i>PTEN</i>	10	89623194	89731687

<i>BLNK</i>	10	97951454	98031333
<i>TLX1</i>	10	102891060	102897546
<i>ADD3</i>	10	111756107	111895323
<i>NUP98</i>	11	3696239	3819022
<i>LMO1</i>	11	8245850	8290182
<i>LMO2</i>	11	33880122	33913836
<i>RAG1</i>	11	36589563	36601310
<i>RAG2</i>	11	36613492	36619829
<i>KMT2A</i>	11	118307204	118397539
<i>ZNF384</i>	12	6775642	6798738
<i>ETV6</i>	12	11802787	12048325
<i>BTG1</i>	12	92534053	92539673
<i>RB1</i>	13	48877882	49056026
<i>TRA</i>	14	22180545	22181065
<i>TRD</i>	14	22564301	22564896
<i>BCL11B</i>	14	99635624	99737822
<i>PAR1</i>	15	25380788	25383200
<i>IGH</i>	16	31973408	31973499
<i>NF1</i>	17	29421944	29704695
<i>IKZF3</i>	17	37913967	38020441
<i>HLF</i>	17	53342320	53402426
<i>TCF4</i>	18	52889562	53303224
<i>TCF3</i>	19	1609291	1652326
<i>MLLT1</i>	19	6210391	6279959
<i>EPOR</i>	19	11487880	11495018
<i>JAK3</i>	19	17935592	17958841
<i>ELL</i>	19	18553472	18632937
<i>RUNX1</i>	21	36160097	36421595
<i>ERG</i>	21	39739182	40033704
<i>TMPRSS2</i>	21	42836477	42880085
<i>BCR</i>	22	23522551	23660224
<i>CRLF2</i>	23	1314886	1331616
<i>CSF2RA</i>	23	1387692	1428828
<i>IL3RA</i>	23	1455508	1501582
<i>P2RY8</i>	23	1581465	1656037

Supplemental Information 3: OGM procedure, OGM-detected aberrations and confirmation of these aberrations with the SOC methods.

After collection of the samples, 15 µl stabilizing buffer (Bionano) was added to 1 ml of bone marrow aspirate (BMA). Samples were stored at -80°C until transported on dry ice to a Bionano certified service provider lab (INRAe, Clermont-Ferrand, France), where the OGM procedure was performed following the manufacturer's instructions. For each sample, 1 mL of BMA was used to purify ultra-high molecular weight (UHMW) DNA using the Bionano Prep SP BMA DNA Isolation kit. Molecules were labeled with the DLS (Direct Label and Stain) DNA Labeling Kit. Saphyr chips were run to reach a minimum yield of 1300 Gb. The *de novo* assembly, RVA and variant annotation pipeline were executed on Solve v.3.7 (Bionano). The *de novo* assembly was run with a coverage of ~200x and the RVA with ~400x mapped reads. Reporting and direct visualization of structural variants was done on Access v.1.7 (Bionano). Filtering of the structural variants was optimized by testing several filter settings. OGM was successfully executed for all 18 bone marrow samples, and 23 aberrations were detected in the regions of interest. In total, 13/23 OGM findings could be confirmed with the SOC methods, and no SOC-detected aberrations were missed by OGM (supplemental table 4).

Supplemental Table 4: OGM-detected aberrations

ID	Referral reason	OGM (splitted per aberration)	De novo / RVA / Both	Reason not detected	SOC	Identified with SOC
BMA1	AML/MDS/MPN	ogm[GRCh37]1q21.1q21.1(144452084_249237532)x2~3 ogm[GRCh37]17p13.1(7,545,377_7,588,071)x1	both <i>de novo</i>	RVA only aberrations >5kb	Karyotyping Could not be confirmed	46,XY,der(13)t(1;13)(q12;p11) -
BMA2	CML	ogm[GRCh37]t(9;22)(q34;q11.2)(133619362_23603312)	both		Karyotyping	46,XY,t(9;22)(q34;q11.2)
BMA3	AML/MDS	ogm[GRCh37]17p13.1(7,545,377_7,588,071)x1	<i>de novo</i>	RVA only aberrations >5kb	Could not be confirmed	-
BMA4	MDS/MPN	ogm[GRCh37](X,1-22)x2 (no aberration)	both		SNP-arrays	arr(X,1-22)x2
BMA5	MDS	ogm[GRCh37](X,Y)x1,(1-22)x2 (no aberration)	both		SNP-arrays	arr(X,Y)x1,(1-22)x2
BMA6	MDS	ogm[GRCh37]17p13.1(7,545,377_7,588,071)x1	<i>de novo</i>	RVA only aberrations >5kb	Could not be confirmed	-
BMA7	MDS/MF	ogm[GRCh37]inv(3)(q25.3q26.2)(160,014,744_168,882,939) ogm[GRCh37]3q25.33(159,902,689-160,014,744)x1 ogm[GRCh37]3q26.2(168,882,939-168,907,480)x1	both both both		Could not be confirmed Could not be confirmed Could not be confirmed	- - -
BMA8	CML	ogm[GRCh37]t(9;22)(q34;q11.2)	both		Karyotyping	46,XX,t(9;22)(q34;q11.2)
BMA9	MDS	ogm[GRCh37]22q11.23;q12.1(23,734,214;29,424,129)x1 ogm[GRCh37]chr21x3	both both		SNP-arrays SNP-arrays	arr[GRCh37] 22q11.23q12.1(23632968_29447635)x1 arr(21)x3
BMA10	MDS/MPN	ogm[GRCh37]inv(15)(q24.1q24.1)(72,959,741_74,362,190) ogm[GRCh37]3p13(71086423_71375386)x1 ogm[GRCh37]9p24.3p13.3(1_35889394)x2 hmz ogm[GRCh37]14q11.2q12(20421719_32361050)x1	both RVA both	RVA not able to detect hmz	Could not be confirmed Could not be confirmed SNP-arrays SNP-arrays	- - arr[GRCh37] 9p24.3p13.3(1_35889394)x2 hmz, 14q11.2q12(20421719_32361050)x1
BMA11	ALL/CLL	ogm[GRCh37](X,Y)x1,(1-22)x2 (no aberration)	both		Karyotyping	46,XY
BMA12	(B)-CLL	ogm[GRCh37]chr12x3	both		SNP-arrays	arr(12)x3
BMA13	MDS	ogm[GRCh37] 20q11.22q13.13(34259243_49502193)x1	both		SNP-arrays	arr[GRCh37] 20q11.22q13.13(34259243_49502193)x1
BMA14	?	ogm[GRCh37](X,Y)x1,(1-22)x2 (no aberration)	both		Karyotyping	46,XY
BMA15	MDS/AML	ogm[GRCh37] fus(5;5)(q14.2;q33.3)	RVA	5% aberrant cells non-cultured	Karyotyping, SNP-arrays	46,XX,5q-[5]/46,XX[5] (only OGM RVA)
BMA16	HCL (CLL)	ogm[GRCh37](X)x1,(1-22)x2 ogm[GRCh37]8p23.3p22(11805_15540773)x1~2 ogm[GRCh37]fus(8;8)(p22;q13.2) ogm[GRCh37]t(14;17)(q32.22;q25.3)(106,249,815;80,915,618)	both both both		Karyotyping SNP-arrays Karyotyping (1:250 metaphases) Could not be confirmed	45,X,-Y[13]/46,XY[7] arr[GRCh37] (Y)x0,8p23.3p22(1_15547178)x1, 8q13.2q24.3(69538276_146364022)x3 fus(8;8)(p22;q13.2),t(14;17)(q32.33;q25.3)
BMA17	MDS	OGM[GRCh37]ins(12p13.2)(11,889,007_11,895,594)	<i>de novo</i>	Disputable OGM breakpoint RVA only aberrations >5kb	Could not be confirmed	-
BMA18	AML	ogm[GRCh37](X,(1-22)x2	both			46,XX[20]

All OGM aberrations detected in a selected group of leukemia patients are depicted in this table. The table also shows if the OGM aberrations are confirmed with the SOC methods.

Abbreviations: ID = sample identification, AML = acute myeloid leukemia, MDS = myelodysplastic syndrome, MPN = myeloproliferative neoplasms, CML = chronic myeloid leukemia, MF = myelofibrosis, ALL = acute lymphoblastic leukemia, CLL = chronic lymphoblastic leukemia, (B)-CLL = B cell acute lymphoblastic leukemia, HCL = hairy cell leukemia, SOC = standard-of-care, OGM = optical genome mapping.

A homozygous region (ogm[GRCh37]9p24.3p13.3(1_35889394)x2 hmz) in sample BMA10 with referral reason myelodysplastic syndrome / myeloproliferative neoplasms was only detected with the *de novo* pipeline because the RVA pipeline cannot detect homozygous regions (Bionano, 30110 Rev K).

A 1.2 kb heterozygous 17p13.1 deletion (ogm[GRCh37]17p13.1(7,545,377_7,588,071)x1) in a 42 kb region that includes *TP53* in samples BMA1, BMA3 and BMA6 and a 1.4 kb heterozygous 12p13.2 insertion in a 6.6 kb region that includes *ETV6* (OGM[GRCh37]ins(12p13.2)(11,889,007_11,895,594)) in sample BMA17 with referral reason myelodysplastic syndrome were only detected with the *de novo* pipeline. The aberrations in BMA1, BMA3, BMA6 and BMA17 were below the resolution of the RVA pipeline (5 kb, Bionano, 30110 Rev K).

A fusion of chromosome 5 (ogm[GRCh37] fus(5;5)(q14.2;q33.3)) in patient BMA15, with referral reason myelodysplastic syndrome / acute myeloid leukemia was only detected with the RVA pipeline. Karyotyping of the aberration identified it as a chromosome 5q deletion in 5 of 10 metaphases. Using SNP-array on non-cultured cells, the estimated percentage of aberrant cells was 5%, which is below the threshold of the *de novo* pipeline (Bionano, 30110 Rev K).

In patient BMA9, with referral reason myelodysplastic syndrome, a 288 kb deletion on chromosome 3 (ogm[GRCh37]3p13(71086423_71375386)x1) with an allele frequency of 3% was only detected with the RVA pipeline. An allele frequency of 3% is below the resolution of the *de novo* pipeline (Bionano, 30110 Rev K). All other aberrations were detected with both pipelines.

In patient BMA16, with referral reason hairy cell leukemia, OGM identified a loss of the p-arm of chromosome 8p23.3p22 (ogm[GRCh37]8p23.3p22(11805_15540773)x1~2) and a chromosome 8 fusion (ogm[GRCh37]fus(8;8)(p22;q13.2)) (table). SNP-array detected a

gain and loss of chromosome 8 (arr[GRCh37](Y)x0,8p23.3p22(1_15547178)x1, 8q13.2q24.3(69538276_146364022)x3), and we performed karyotyping to confirm the fusion. The fusion was detected in only 1 of 250 metaphases, probably due to the loss of aberrant mature B cells in the culturing procedure (1). The clinical significance of the fusion is unknown (2,3).

In patient BMA1, with referral reason acute myeloid leukemia / myelodysplastic syndrome / myeloproliferative neoplasms, karyotyping confirmed a gain of 1q21.1q21.1 (ogm[GRCh37]1q21.1q21.1(144452084_249237532)x2~3) as a 46,XY,der(13)t(1;13)(q12;p11) with karyotyping.

References Supplemental Information 3

1. Troussard X, Cornet E. Hairy cell leukemia 2018: update on diagnosis, risk-stratification, and treatment. *Am J Hematol.* 2017;12:1382-1390.
2. The 1000 Genomes Project Consortium. A global reference for human genetic variation. *Nature* 2015;526(7571):68-74.
3. Edelmann J, Holzmann K, Miller F, Winkler D, Bühler A, Zenz T et al. High-resolution genomic profiling of chronic lymphocytic leukemia reveals new recurrent genomic alterations. *Blood* 2012;120(24):4783-4794.

Supplemental Information 4:

Supplemental Table 5: Crispr locations.

ID	Additional putative OGM aberration	Gene	crRNA GRCh37 hg19
BMA1	OGM[GRCh37]17p13.1(7,545,377_7,588,071)x1	<i>TP53</i>	chr17:7,543,974-7,543,993 +
BMA3	OGM[GRCh37]17p13.1(7,545,377_7,588,071)x1	<i>TP53</i>	chr17:7,559,625-7,559,644 -
BMA6	OGM[GRCh37]17p13.1(7,545,377_7,588,071)x1	<i>TP53</i>	chr17:7,556,557-7,556,576 + chr17:7,576,982-7,577,001 - chr17:7,572,406-7,572,425 + chr17:7,589,483-7,589,502 -
BMA9	OGM[GRCh37]3p13(71,086,423_71,375,386)x1	<i>FOXP1</i>	chr3:71,082,359-71,082,378 + chr3:71,101,049-71,101,068 - chr3:71,082,955-71,082,974 + chr3:71,101,401-71,101,420 - chr3:71,371,938-71,371,957 + chr3:71,384,613-71,384,632 - chr3:71,368,075-71,368,094 + chr3:71,382,344-71,382,363 -
BMA17	OGM[GRCh37]ins(12p13.2)(11,889,007_11,895,594)	<i>ETV6</i>	chr12:11,888,244-11,888,263 + chr12:11,902,197-11,902,216 - chr12:11883363-11883382 + chr12:11910042-11910061 -
BMA16	OGM[GRCh37]t(14;17)(q32.22;q25.3) (106,249,815;80,915,618)	<i>IGHG1</i>	chr17:80967365-80967384 + chr17:80996130-80996149 + chr14:106126211-106126230 - chr14:106100173-106100192 - chr14:106083832-106083851 -
BMA7	OGM[GRCh37]inv(3)(q25.33;q26.2)(160,014,744_168,882,939) OGM[GRCh37]3q25.33(159,902,689-160,014,744)x1 OGM[GRCh37]3q26.2(168,882,939-168,907,480)x1	<i>MECOM</i>	chr3:159898486-159898505 + chr3:160032530-160032549 -
BMA9	OGM[GRCh37]inv(15)(q24.1;q24.1)(72,959,741_74,362,190)	<i>PML</i>	chr15:72975831-72975850 - chr15:72966403-72966422 -

For each additional OGM-detected putative aberration, this table lists the sample ID, the genes involved and the GRCh37 coordinates of the crRNA enzymes.