Supplementary Information: Distinction of lymphoid and myeloid clonal hematopoiesis

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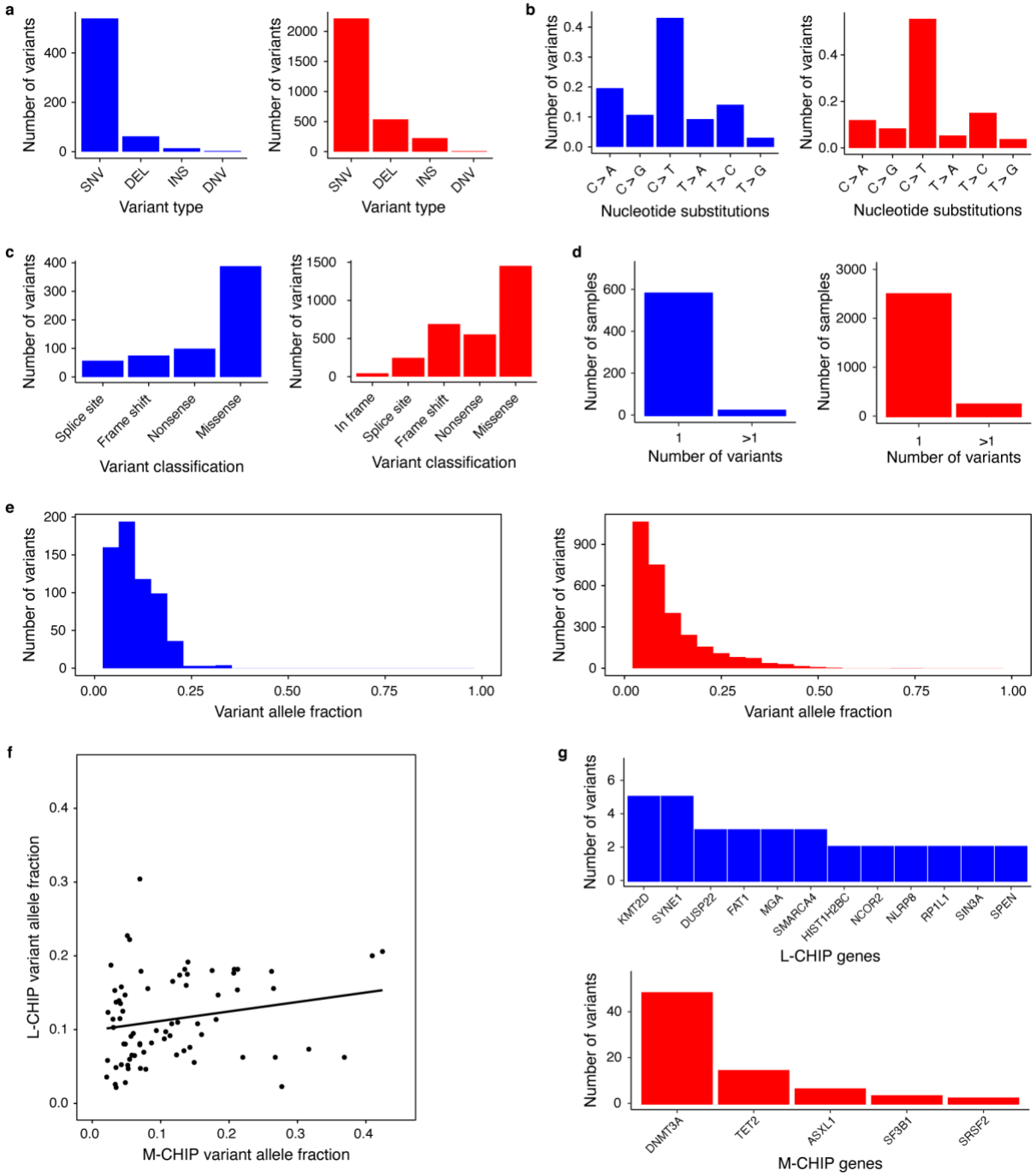
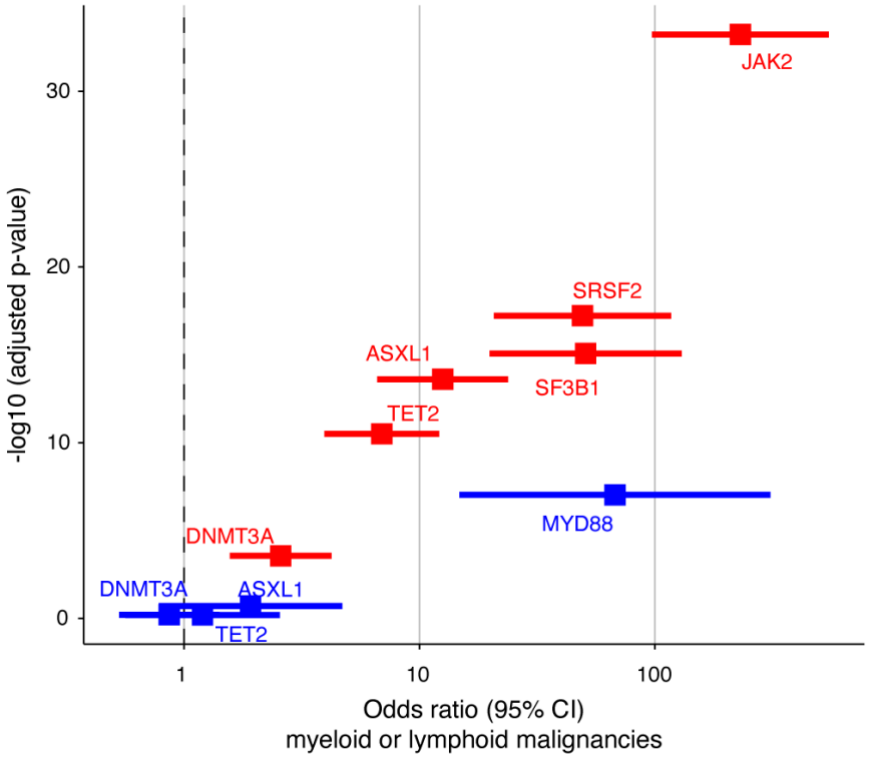
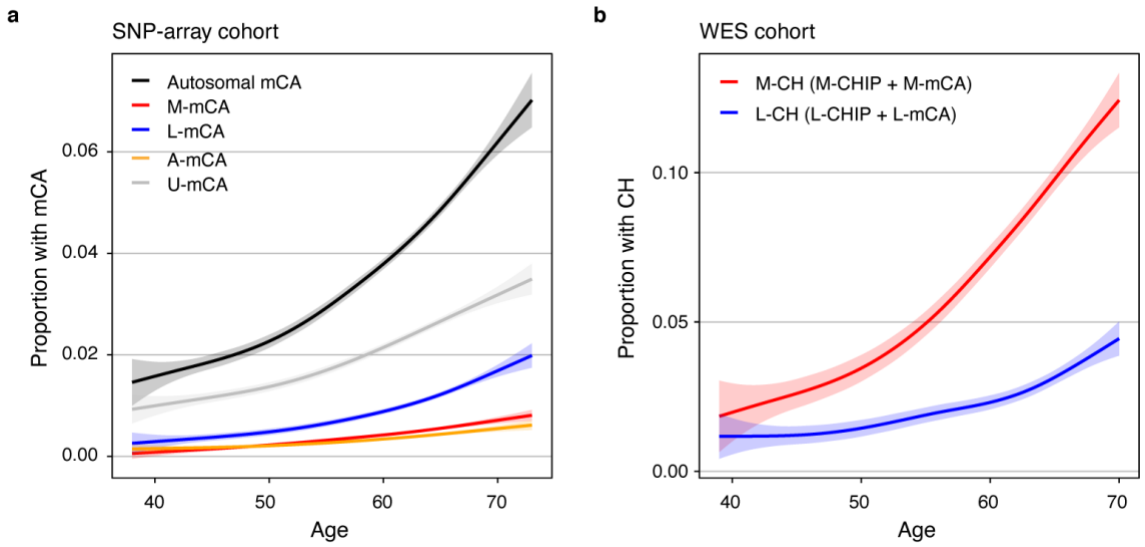
Supplementary Figures



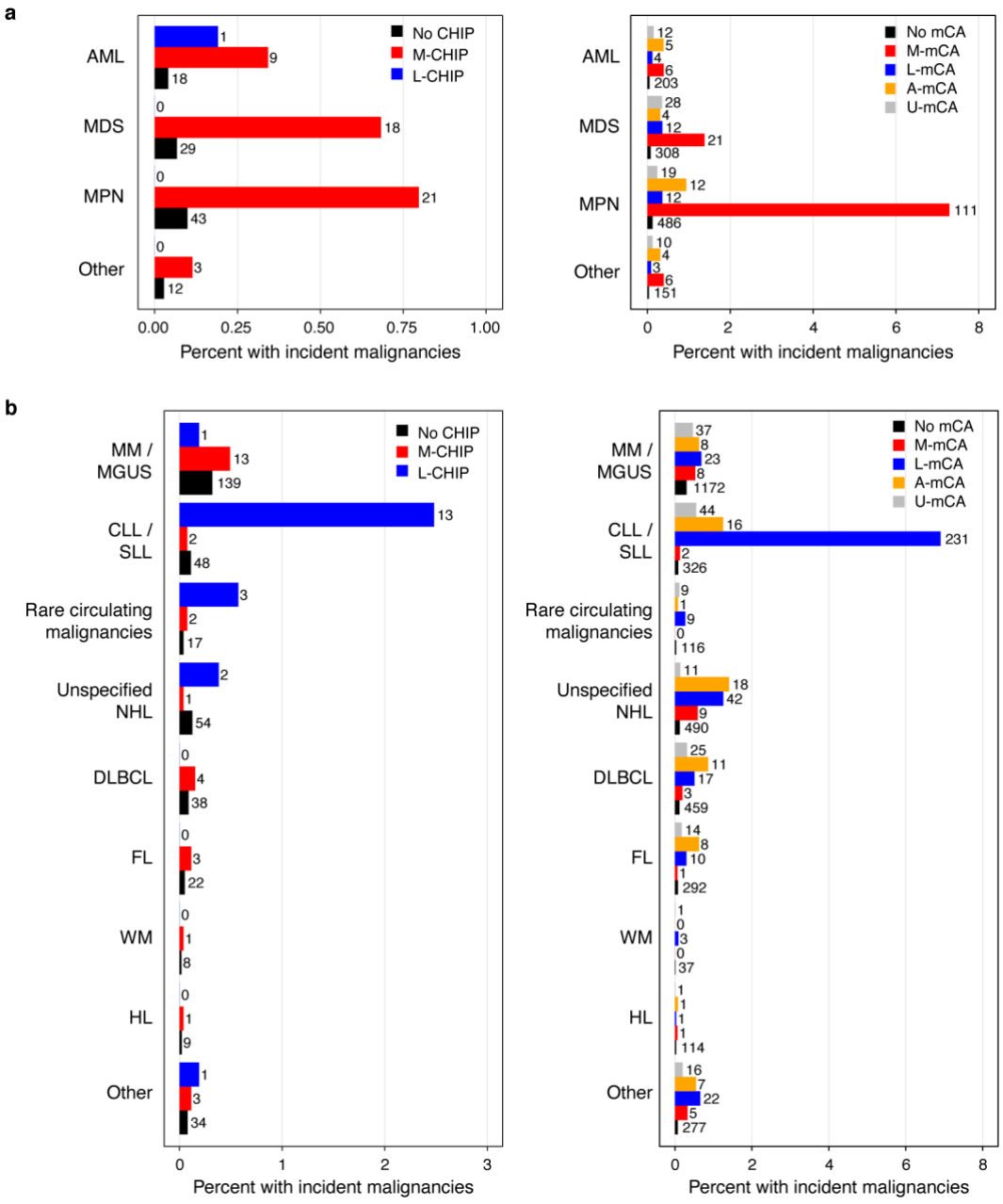
Supplementary Figure S1: Characteristics of somatic variants detected in myeloid and lymphoid driver genes. a) variant type, **b)** nucleotide substitutions for single nucleotide substitutions, **c)** variant classification based on changes in canonical protein sequence, **d)** number of variants detected per individual, **e)** variant allele fraction (VAF) of variants. Characteristics of M-CHIP are shown in red and L-CHIP in blue. **f)** Correlation between clone sizes of M-CHIP and L-CHIP detected in the same individual (n=73). **g)** Myeloid and lymphoid genes mutated among individuals carrying both M-CHIP and L-CHIP.



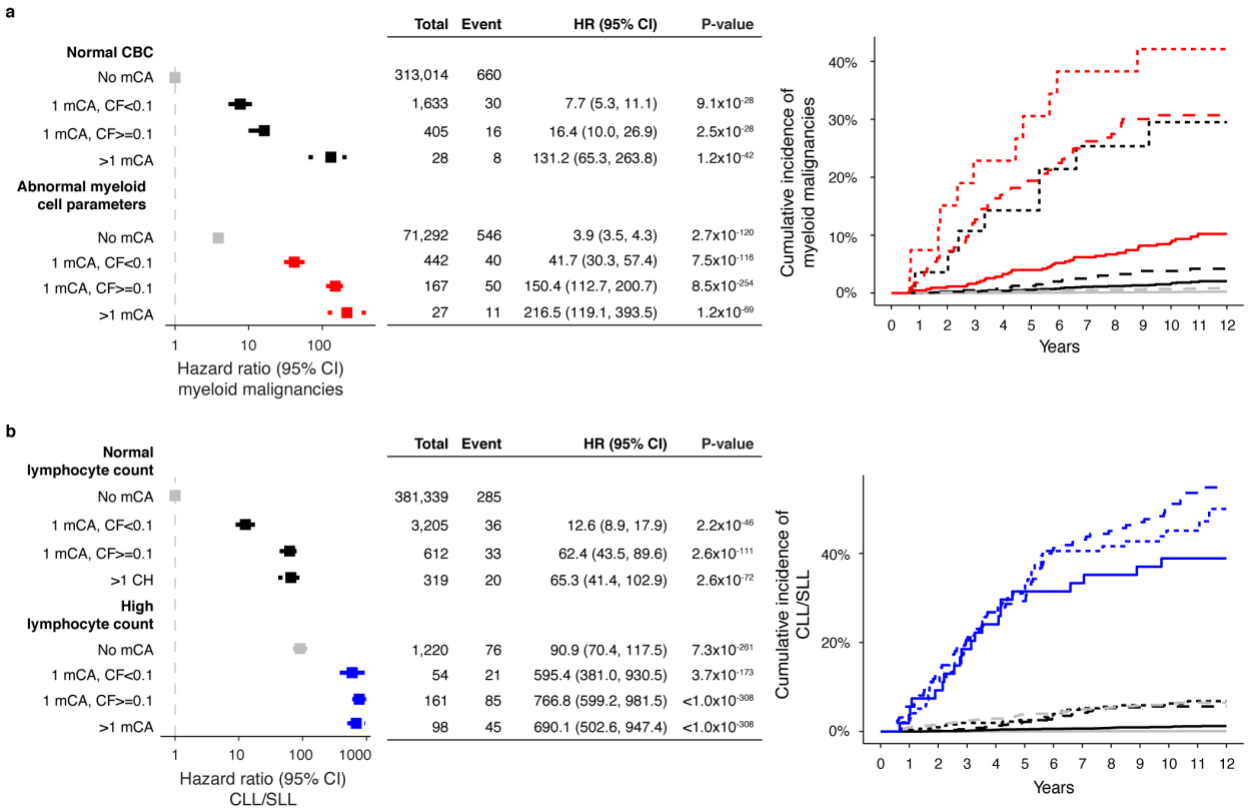
Supplementary Figure S2: Enrichment of CHIP gene mutations in myeloid and lymphoid malignancies. CHIP genes associated with myeloid (red) and lymphoid (blue) malignancies. Only genes mutated in at least 3 individuals who developed an incident myeloid or lymphoid malignancy between six months and 12 years after blood sample collection were analyzed. Tested genes were *DNMT3A* (n=1,827, n myeloid malignancies=18, and n lymphoid malignancies=17), *TET2* (n=510, n myeloid malignancies=14, and n lymphoid malignancies=7), *ASXL1* (n=201, n myeloid malignancies=11, and n lymphoid malignancies=5), *SRSF2* (n=34 and n myeloid malignancies=7), *SF3B1* (n=28 and n myeloid malignancies=6), *JAK2* (n=23, n myeloid malignancies=11), and *MYD88* (n=7, n lymphoid malignancies=3). Data are presented as odds ratio and 95% confidence intervals, computed by generalized linear regression model adjusting for age, age squared, sex, and smoking. CI, confidence interval.



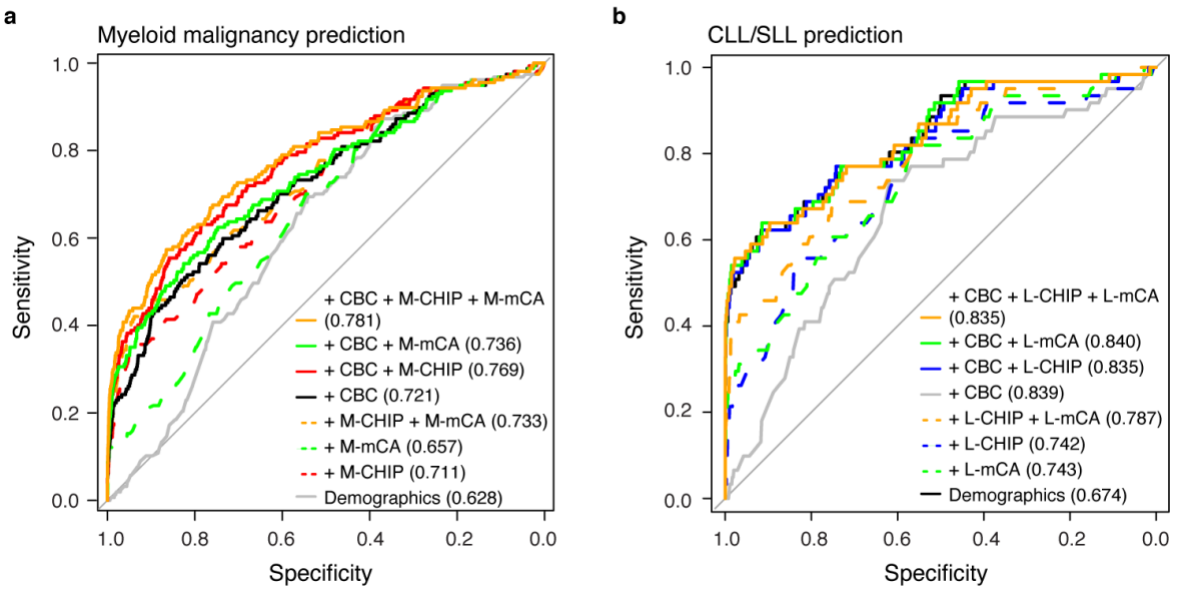
Supplementary Figure S3: Prevalence of CH increases with age. a) All four categories of mCAs are associated with age. The A-mCA (n=1278) is the rarest category of mCAs followed by M-mCA (n=1523), and L-mCA (3345). A large fraction of the mCAs remained unclassified (U-mCA, n=7966). **b)** Frequency of myeloid CH (M-CHIP + M-mCA, n=2975) and lymphoid CH (L-CHIP + L-mCA, n=1045) in the UKB WES cohort. (**a**-**b**) Data is fit with the general additive model using cubic regression splines and the shaded bands indicate the estimated 95% confidence interval.



Supplementary Figure S4: Enrichment of myeloid and lymphoid malignancy sub-types among individuals with CH. a) Frequencies of myeloid malignancy sub-types among CH cases and controls. **b)** Frequencies of lymphoid malignancy sub-types among CH cases and controls. The numbers above the bars indicate the total number of individuals with incident malignancy in those groups. The individuals are categorized based on the first coded hematologic malignancies. MDS, myelodysplastic syndrome; AML, acute myeloid leukemia; MPN, myeloproliferative neoplasms; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; MM, multiple myeloma; MGUS, monoclonal gammopathy of undetermined significance; NHL, non-Hodgkin's lymphoma; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma; WM, Waldenstrom's macroglobulinaemia; HL, Hodgkin's lymphoma; U-mCA, unclassified mCAs.



Supplementary Figure S5: Integration of mCA and blood cell indices stratify risk for developing hematologic malignancies. a) Myeloid CH (M-mCA/A-mCA) and abnormal myeloid cell parameters increase risk of myeloid malignancies. **b)** Lymphoid CH (L-mCA/A-mCA) and elevated lymphocyte count increase risk of CLL/SLL. (**a-b**) Since A-mCA were associated with risk of both myeloid and lymphoid malignancies, these are combined with M-mCA in the analysis of myeloid malignancies and with L-mCA in the analysis of lymphoid malignancies. Data are presented as hazard ratio and 95% confidence intervals, computed by using Cox proportional hazards model adjusting for age, sex, smoking, genetic ethnic ancestry, and genetic principal components 1-5. Red blood cell counts, platelet counts, and neutrophil counts were used to define individuals with abnormal myeloid cell parameters. CBC, complete blood count; HR, hazard ratio; CI, confidence interval; CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; VAF, variant allele fraction; CF, cell fraction.



Supplementary Figure S6: **Integration of CH abnormalities and CBC predict the risk of myeloid malignancies and CLL/SLL. a**) Sensitivity and specificity for predicting the incidence of myeloid malignancies computed by 10-fold cross-validation. Individuals with a diagnosis of myeloid malignancy (n=157) and those that did not have a diagnosis of myeloid or lymphoid malignancies (n=44781) were used for training and testing. **b**) Sensitivity and specificity for predicting the incidence of CLL/SLL computed by 10-fold cross-validation. Individuals with a diagnosis of CLL or SLL (n=61) and those that did not have a diagnosis of myeloid or lymphoid malignancies (n=44781) were used for training and testing. (**a-b**) Baseline predictor included demographic characteristics (age, sex, smoking status, and genetic ethnic ancestry). CHIP (number of CHIP mutations and maximum VAF), mCA (number of alterations and maximum cell fraction), and CBC were added as predictors together with demographics. The values inside the parentheses indicate the AUC. Since A-mCA were associated with risk of both myeloid and lymphoid malignancies, these are combined with M-mCA in the analysis of myeloid malignancies and with L-mCA in the analysis of lymphoid malignancies. CLL, chronic lymphocytic leukemia; SLL, small lymphocytic lymphoma; CBC, complete blood count; VAF, variant allele fraction; AUC, area under the curve.

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