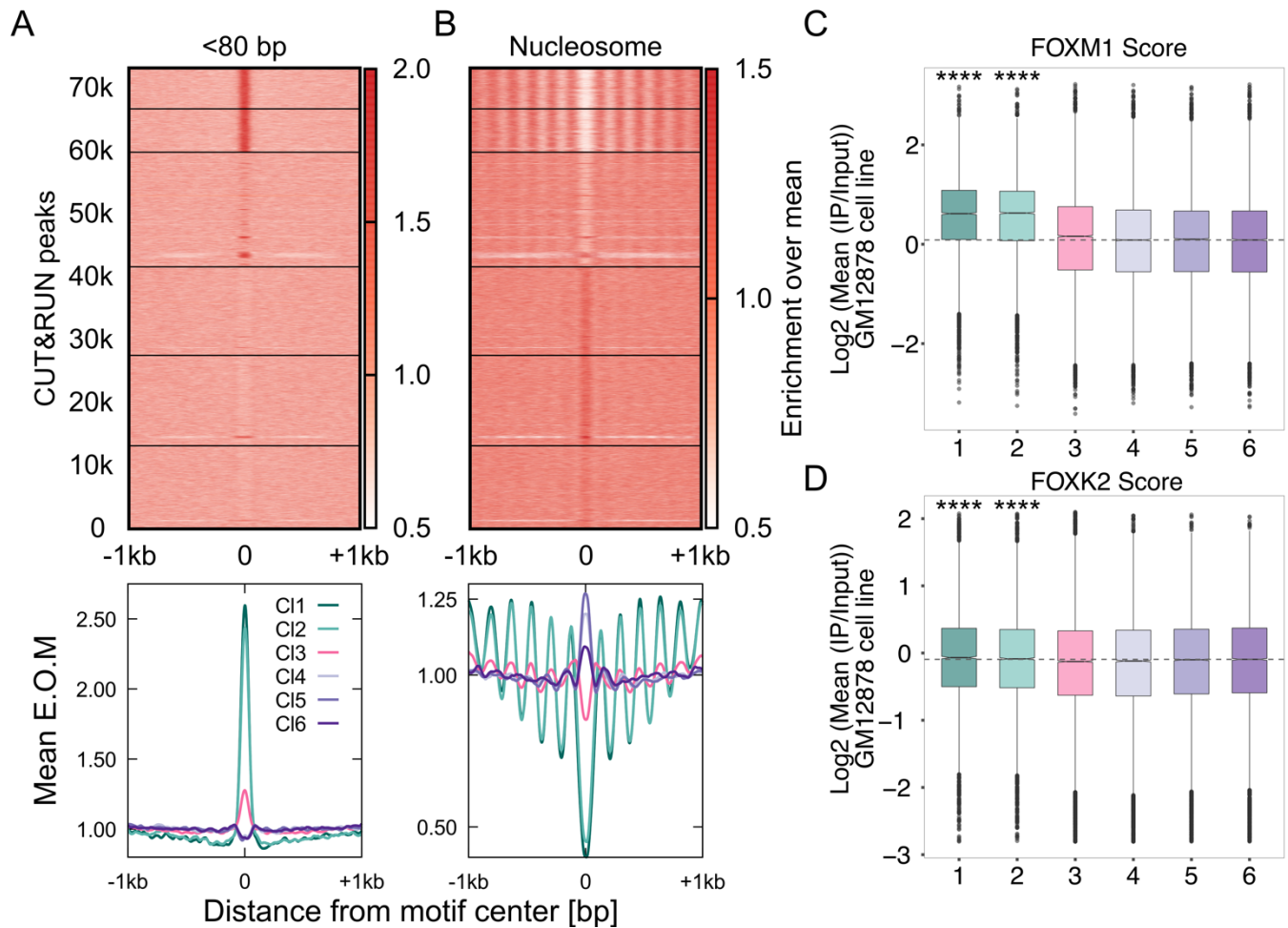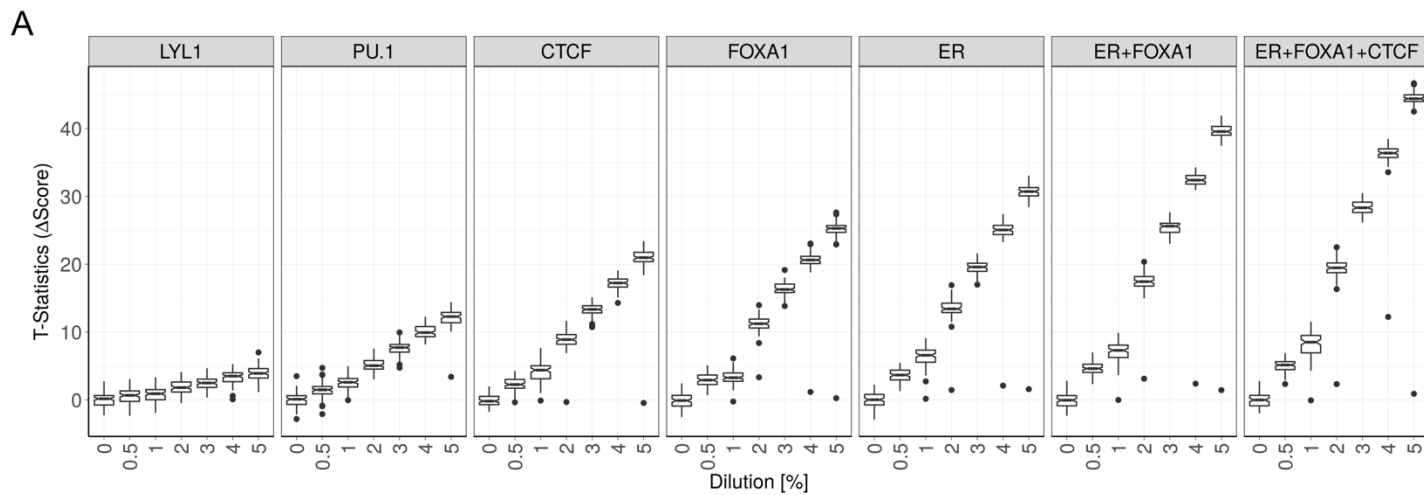**Figure S1. Dilution of PU.1 TF footprints due to presence of cancer. A)** K-means clustering is performed on smoothed length distribution to group TFBSs with similar cfDNA fragment length distribution. Here, smoothened length distributions of clusters of PU.1 TFBS are shown. Weighted length (W.L.) for each PU.1 length cluster is shown in parentheses. **B)** Enrichment over the mean signal in TFBS ± 1Kb of cfDNA short (<80 bp) fragments is plotted as a heatmap (**top**, 53,008 PU.1 TFBS) and as metaplots for each cluster (**bottom**; the horizontal green line is drawn at the maximum mean E.O.M (enrichment over mean) observed IH02) **C)** Same as (B) for nucleosomal sized fragments. Horizontal line in the metaplot (bottom) is drawn at the minimum mean E.O.M observed in when IH02 cfDNA is mapped at PU.1 sites **D)** Mapping of ChIP scores from GM12878 cell line to length clusters. Number of sites (n) in length clusters and p-value using KS test are: Cl1: n = 7440, p (1,6) = 0.087; Cl2: n = 8032, p (2,6) = 0.58; Cl3: n = 9503, p (3,6) = 0.24; Cl4: n = 9254, p (4,6) = 0.93; Cl5: n = 8848, p (5,6) = 0.85; Cl6: n = 9931 **E-H)** Same as A-D when UCD65 ctDNA is mapped to PU.1 sites (n = 39,841). For (H) Number of sites (n) in length clusters and p-value using KS test are: Cl1: n = 5847, p (1,6) = 0.088; Cl2: n = 6537, p (2,6) = 0.093; Cl3: n = 6021, p (3,6) = 0.14; Cl4: n = 5346, p (4,6) = 0.26; Cl5: n = 8524, p (5,6) = 0.28; Cl6: n = 7566
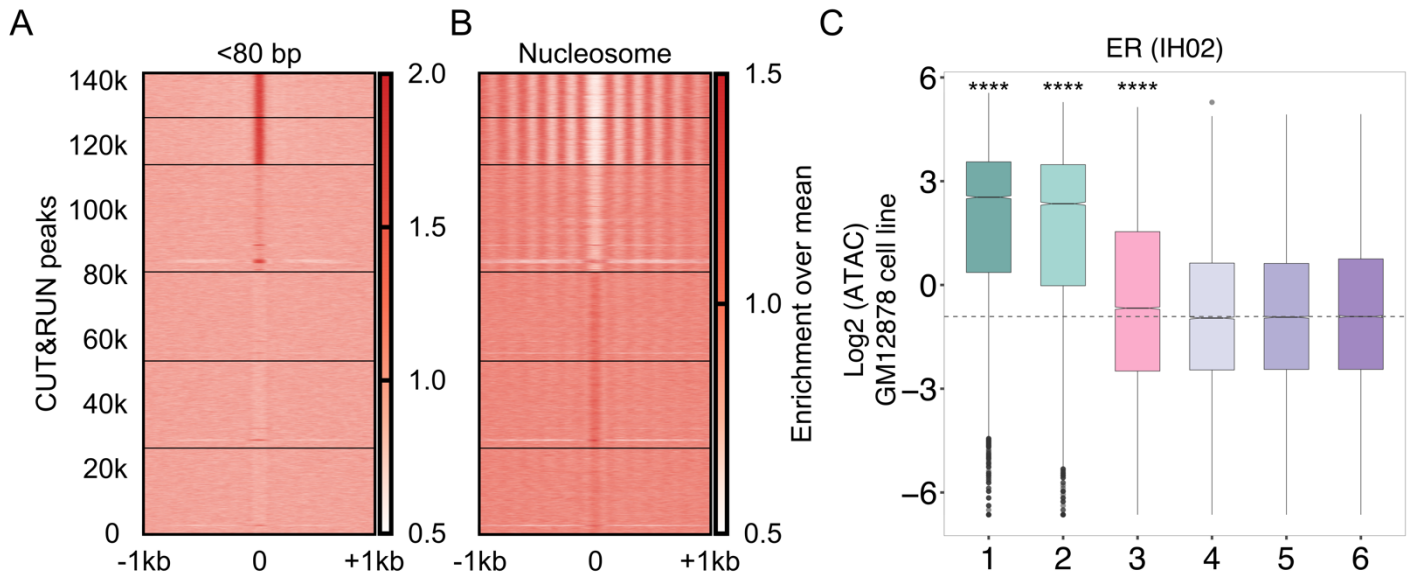
Figure S2. ER binding inferred in hematopoietic cells. **A)** Enrichment over the mean signal in TFBS ± 1Kb of cfDNA short (<80 bp) fragments is plotted as a heatmap (14,2202 ER CUT&RUN peaks) **B)** Same as **(A)** for nucleosomal sized (130-180 bp) fragments **C)** Boxplot of ATAC scores (Log2) from GM12878 cell line. Number of sites (n) in length clusters and p-value using KS test are: Cl1: n = 13539, p (1,6) < 2.2 x10^{-16}; Cl2: n = 14586, p (2,6) < 2.2 x10^{-16}; Cl3: n = 33137, p (3,6) = 1.3 x 10^{-76}; Cl4: n = 27534, p (4,6) = 0.23; Cl5: n = 26957, p (5,6) = 0.93; Cl6: n = 26449

Figure S3. FOXM1 binding in healthy plasma at FOXA1 binding sites inferred from ER+ tumor. A) Enrichment over the mean signal in TFBS ± 1Kb of cfDNA short (<80 bp) fragments is plotted as a heatmap (**top;** 72,938 FOXA1 CUT&RUN peaks) and as a metaplot (**bottom**) **B)** Same as (A) for nucleosomal sized fragments (130-180 bp) **C)** Boxplot of FOXM1 ChIP scores from GM12878 cell line mapped to cfDNA length clusters. Number of sites (n) in length clusters and p-value using KS test are: Cl1: n = 6351, p (1,6) = 2.4 x10^{-290}; Cl2: n = 6871, p (2,6) = 6 x10^{-259}; Cl3: n = 18216, p (3,6) = 0.01; Cl4: n = 14075, p (4,6) = 0.23; Cl5: n = 14375, p (5,6) = 0.92; Cl6: n = 13050. **D)** Boxplot of FOXK2 ChIP scores from GM12878 cell line mapped to cfDNA length clusters. n and p are: Cl1: n = 6351, p (1,6) = 1.2 x10^{-20}; Cl2: n = 6871, p (2,6) = 2.2 x10^{-11}; Cl3: n = 18216, p (3,6) = 0.46; Cl4: n = 14075, p (4,6) = 0.52; Cl5: n = 14375, p (5,6) = 1; Cl6: n = 13050

A

Figure S4. Boxplots of T-statistics performed on ΔScore at different TF sites (individual or in combination) for 100 bootstraps at a given dilution.
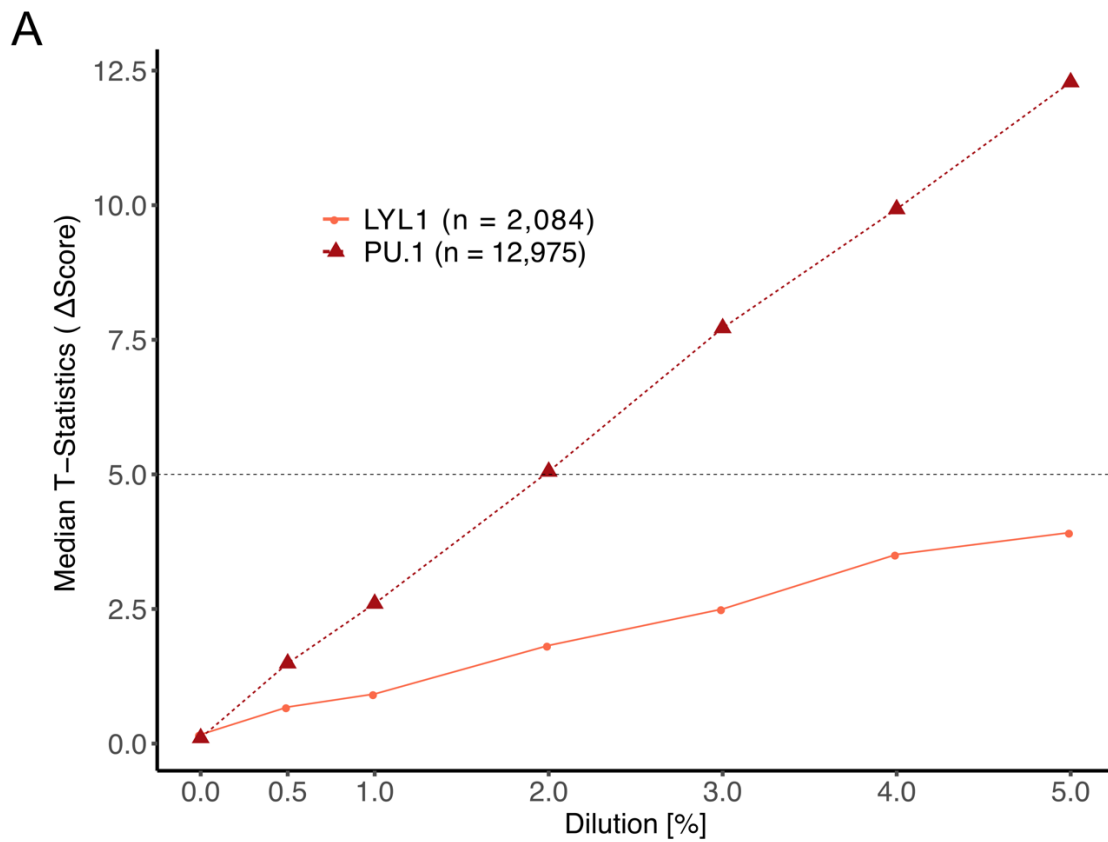
Figure S5. Median t-statistics line plot for PU.1 and LYL1.

Table S1. Plasma samples used in this study.

Sample name	Source name	Sex	Disease status
MCF7	Cell line	F	ER+ breast cancer
UCD4	Breast tumor xenograft	F	Breast cancer with ER mutation
UCD65	Breast tumor xenograft	F	Breast cancer with ER amplification
F02	Cell-free DNA	F	Healthy
F05	Cell-free DNA	F	Healthy
SporeD3	Cell-free DNA	M	Healthy
BC02	Cell-free DNA	F	ER+ breast cancer
BC03	Cell-free DNA	F	ER+ breast cancer
SporeA2	Cell-free DNA	M	Lung cancer (non-small)
SporeB2	Cell-free DNA	F	Lung cancer (small cell)
SporeF2	Cell-free DNA	M	Lung cancer (squamous)
SporeG2	Cell-free DNA	M	Lung cancer (Adenocarcinoma)

Table S2. Transcription Factor ChIP-seq Peak Counts.

Category	CTCF	PU.1	LYL1
Total ChIP peaks	231,309	67,558	33,709
Chr1-X	231,075	67,502	33,681
After blacklisted region filtering	230,965	67,496	33,608
Motif discovery	215,818	71,205	14,899
Overlapping motifs in +- 50 bp	97,229	17,216	6,853
Non-overlapping motif	**118,589**	**53,989**	**8,046**