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(54) DE NOVO CHARACTERIZATION OF CELL-FREE DNA FRAGMENTATION HOTSPOTS IN HEALTHY AND EARLY-STAGE CANCERS

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(2) Date: Dec. 21, 2022

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G16B 40/00 (2019.01)

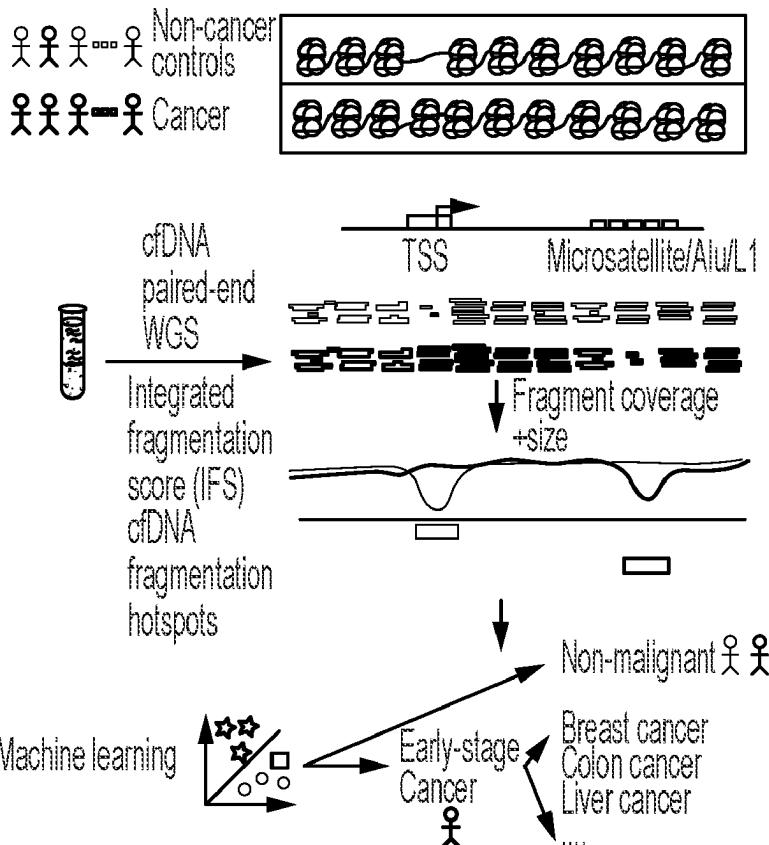
G16H 50/20 (2018.01)

(52) U.S. Cl.

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ABSTRACT

A system and method for identifying genomic regions with higher fragmentation rates than the local and global backgrounds as part of diagnosing early stage cancer is provided. The method includes steps of: de-novo characterizing genome-wide cell-free DNA fragmentation regions with higher fragmentation rates than the local and global backgrounds from whole-genome sequencing by weighing the fragment coverages in each region by a ratio of average fragment sizes in the region versus that in the whole chromosome to generate a score; and identifying DNA fragmentation regions of interest based upon comparing the score with a threshold. The system and method can utilize identified DNA fragmentation hotspots for the detection and localization of multiple early-stage cancers (or certain other non-malignant disease).



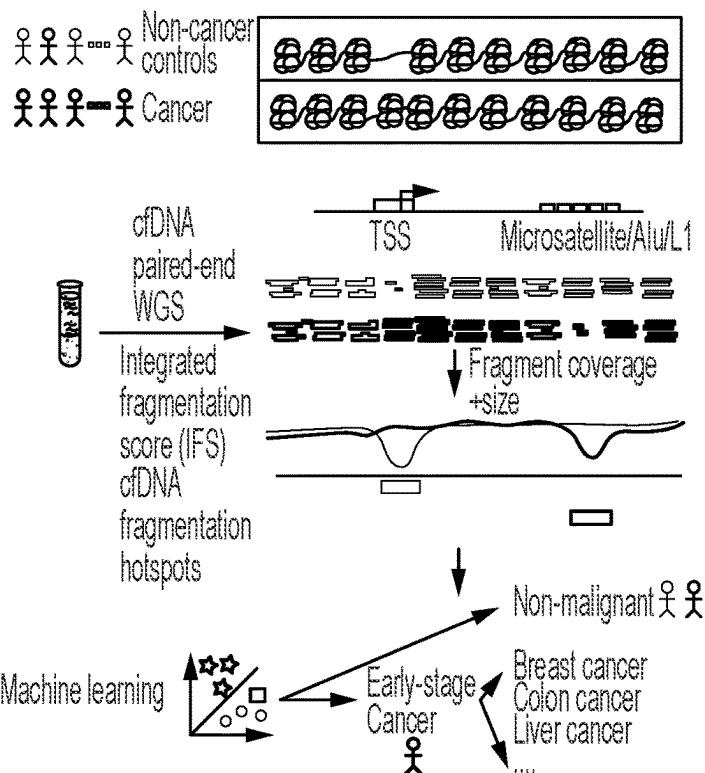


FIG. 1a

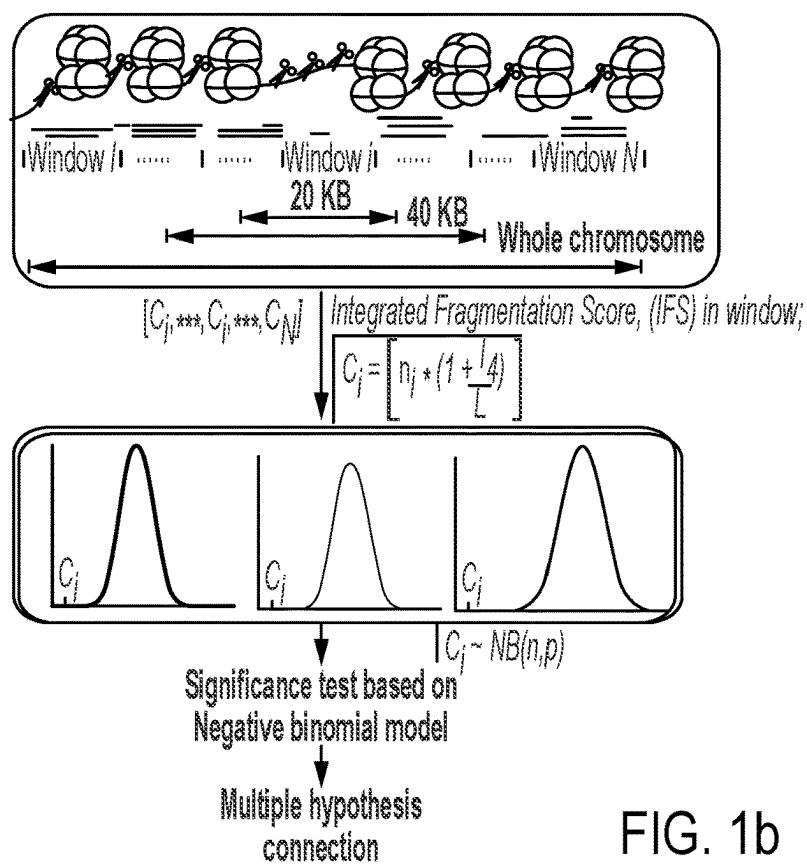


FIG. 1b

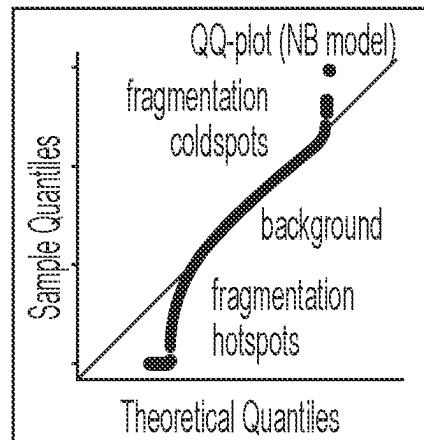


FIG. 1c

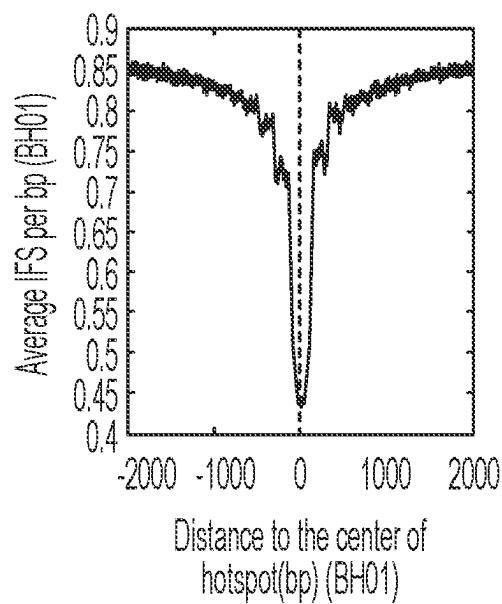


FIG. 1d

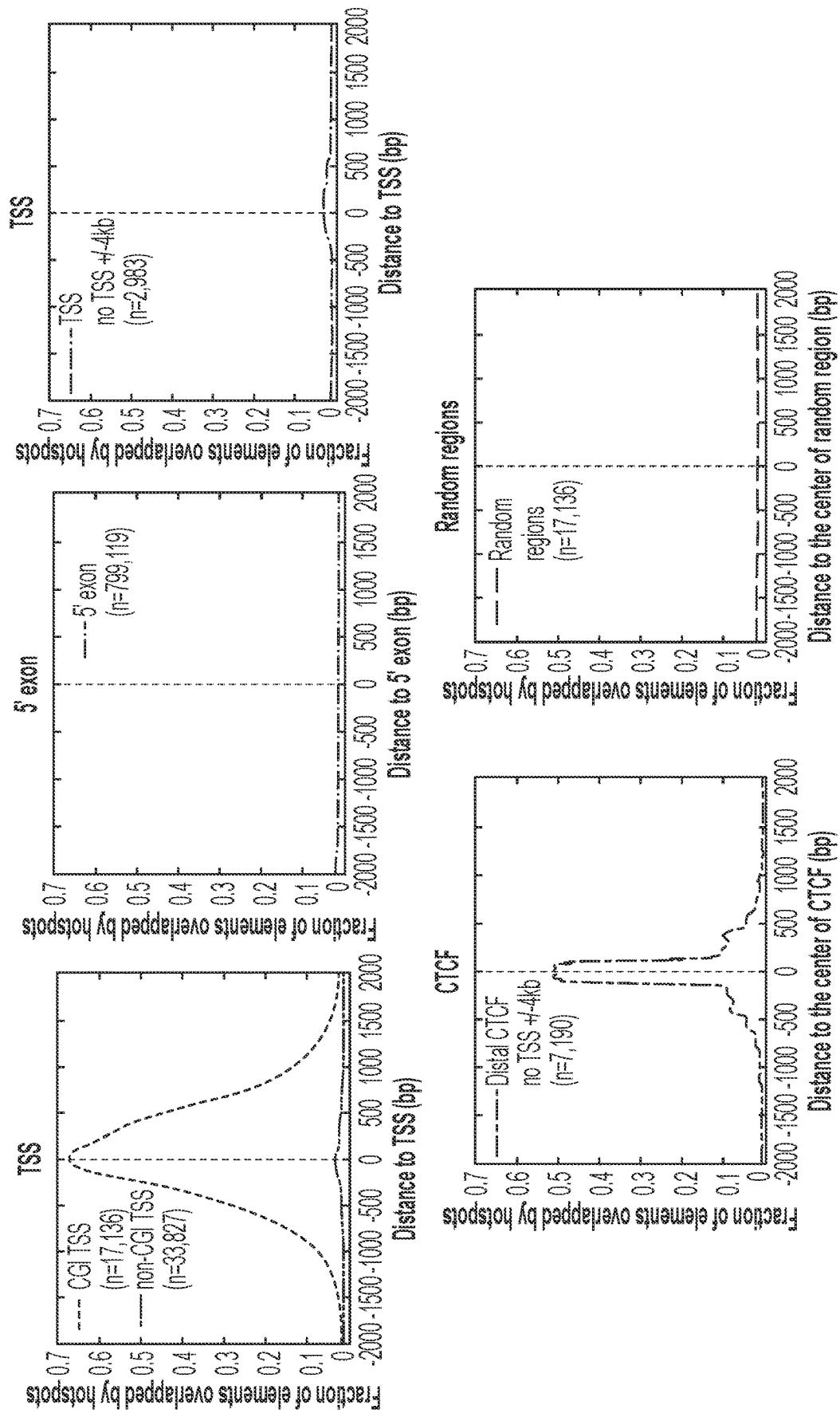


FIG. 2a

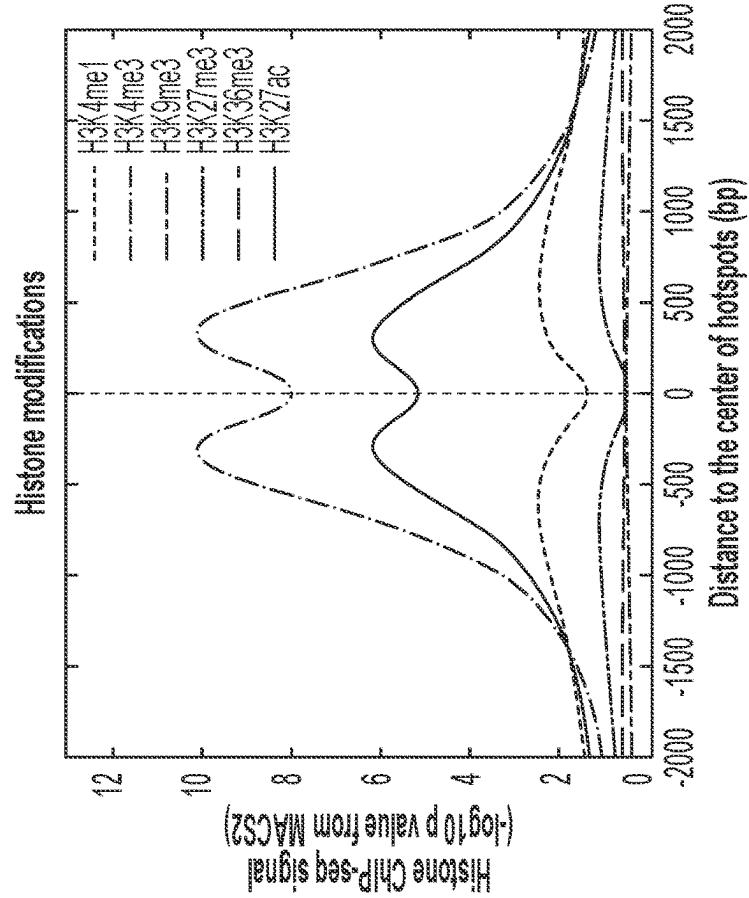


FIG. 2c

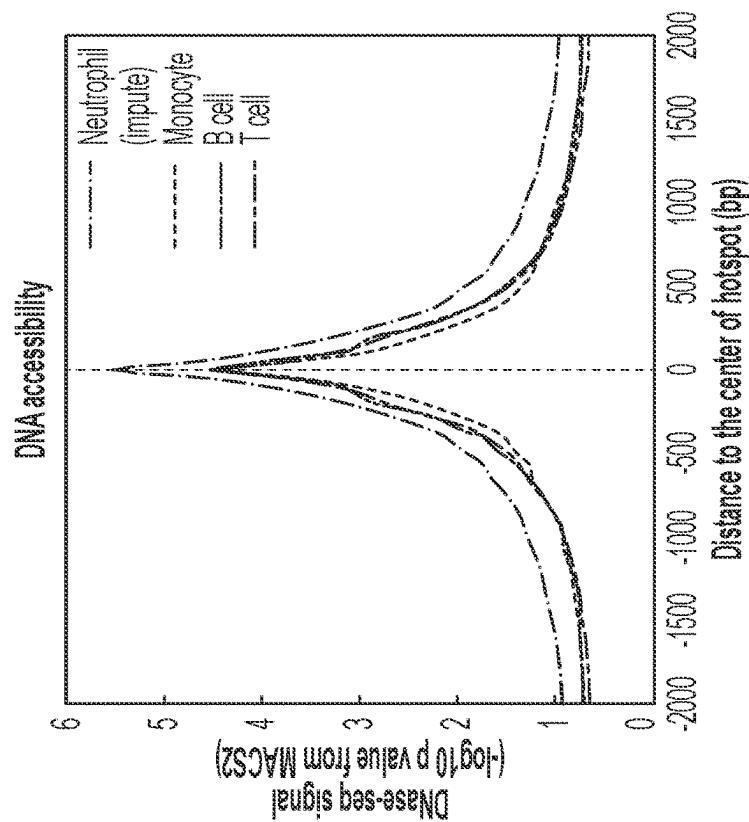


FIG. 2b

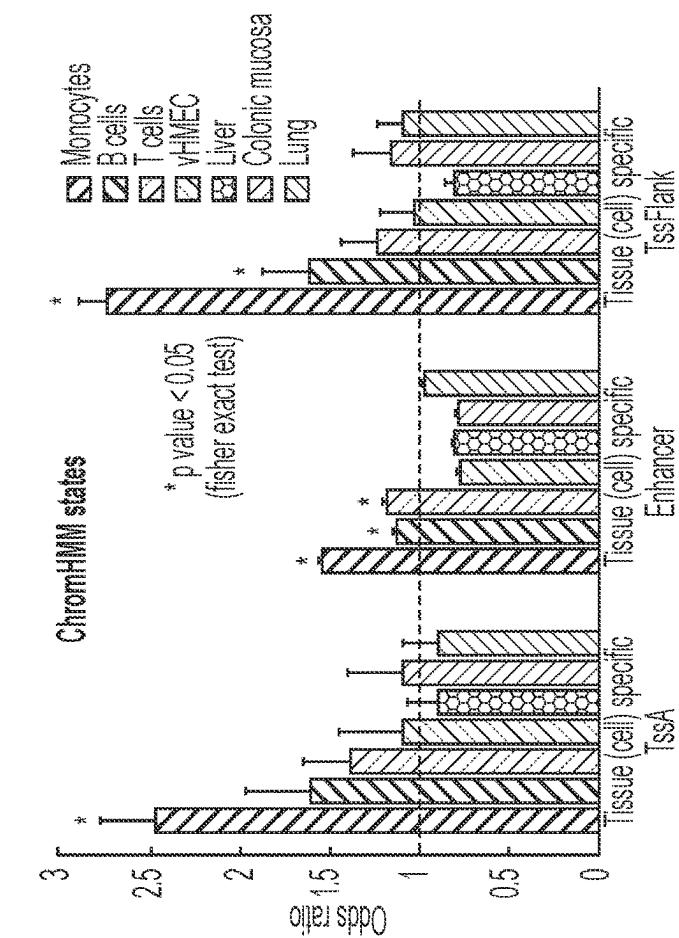


FIG. 2e

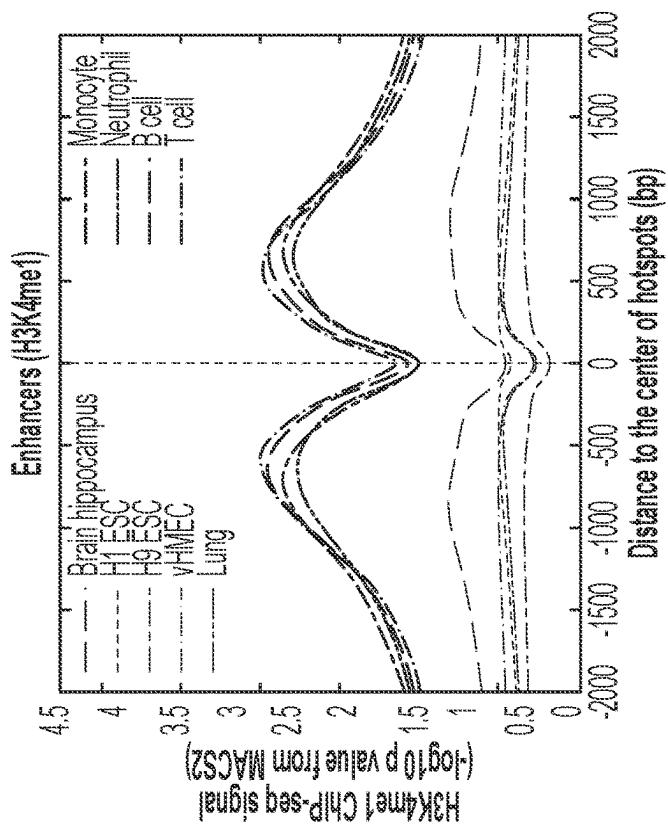


FIG. 2d

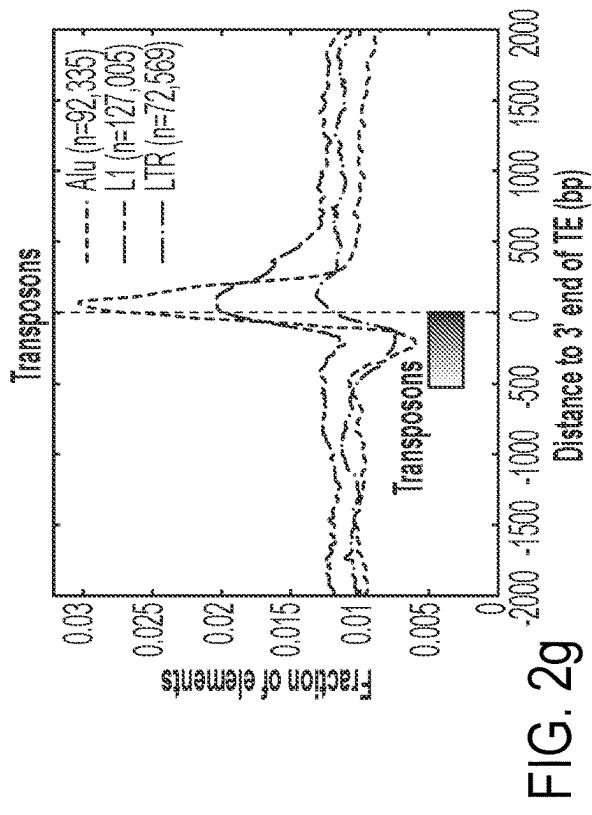
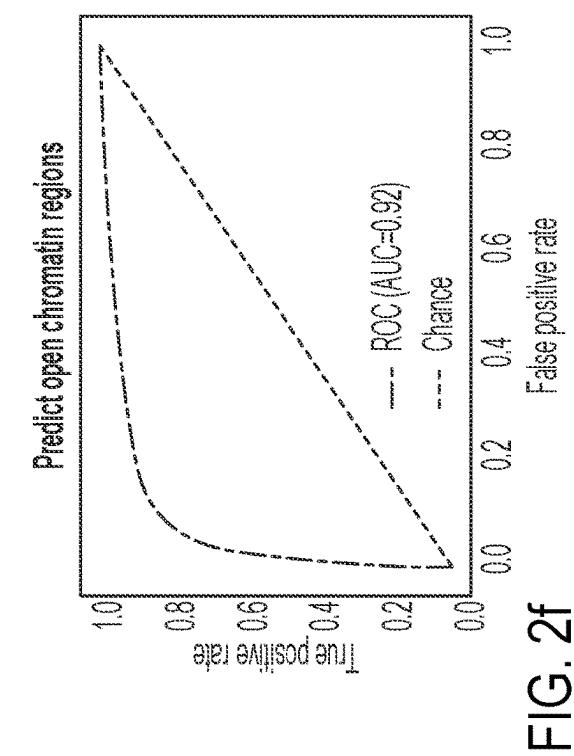
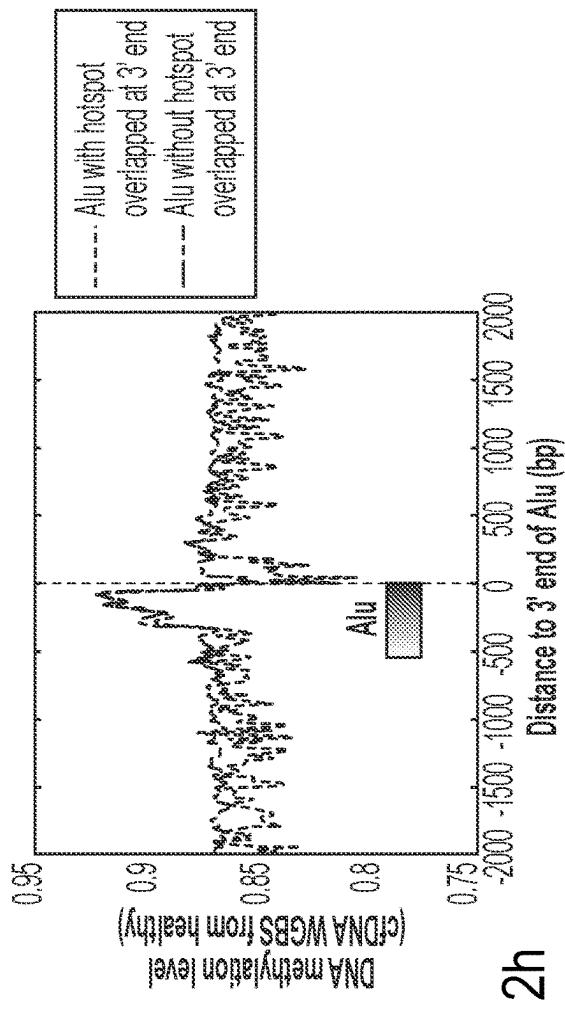


FIG. 2g



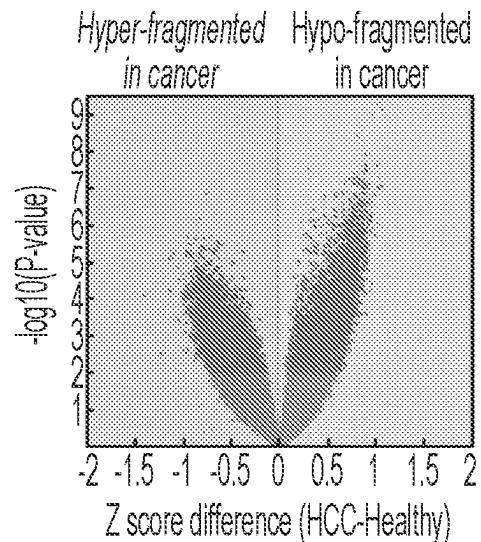


FIG. 3a

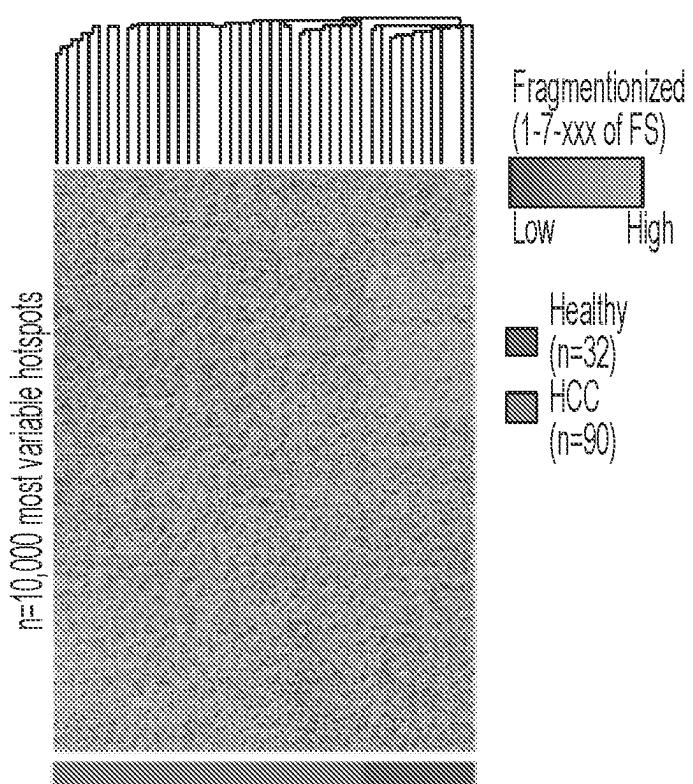
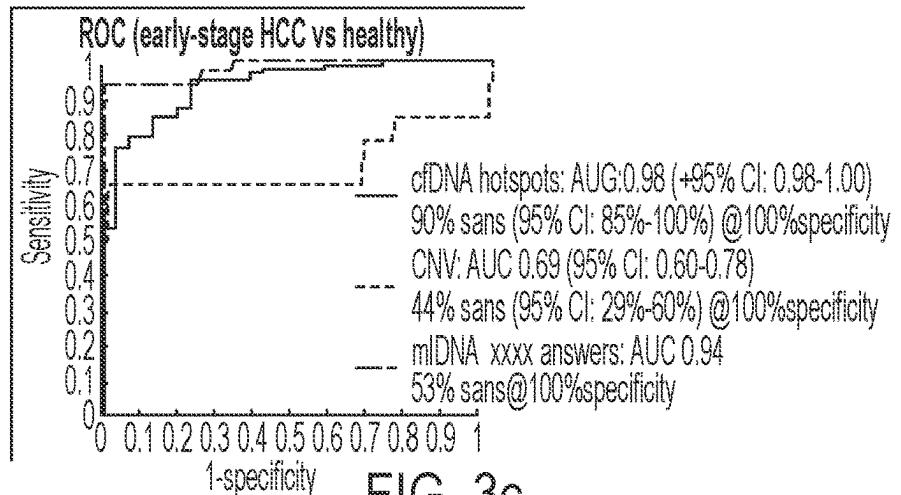
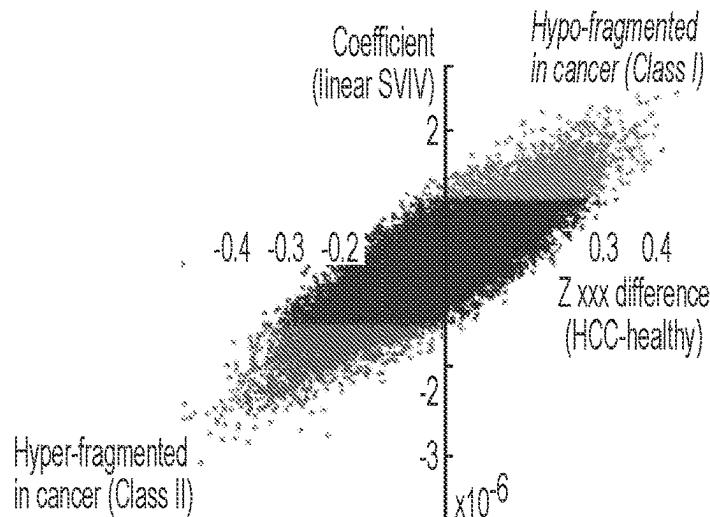
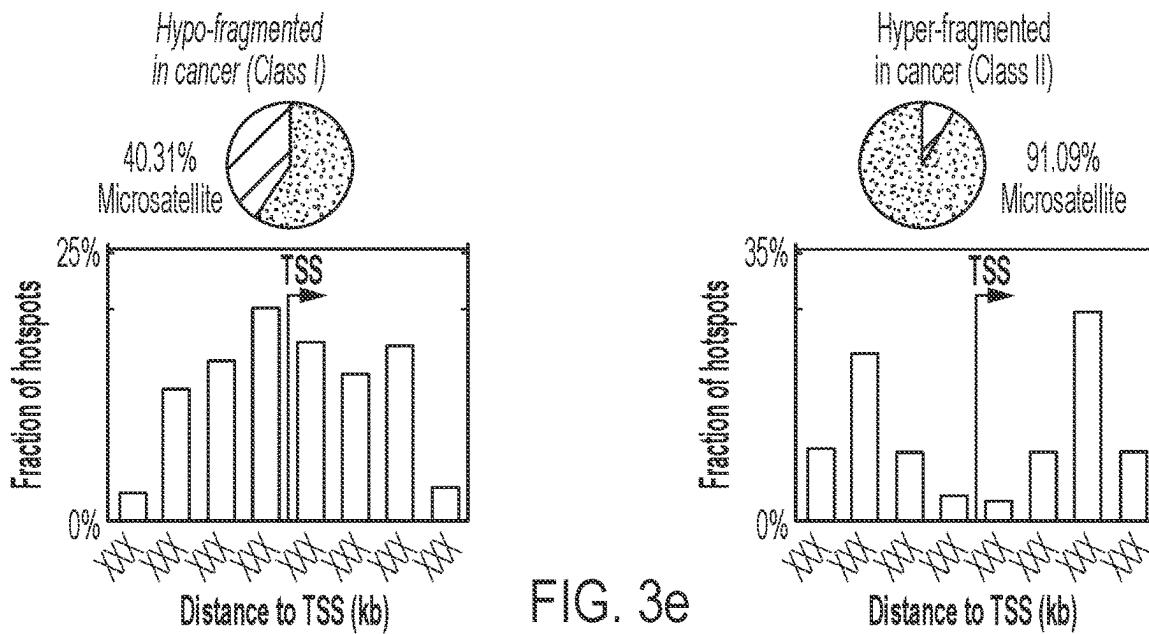


FIG. 3b

**FIG. 3c****FIG. 3d****FIG. 3e**

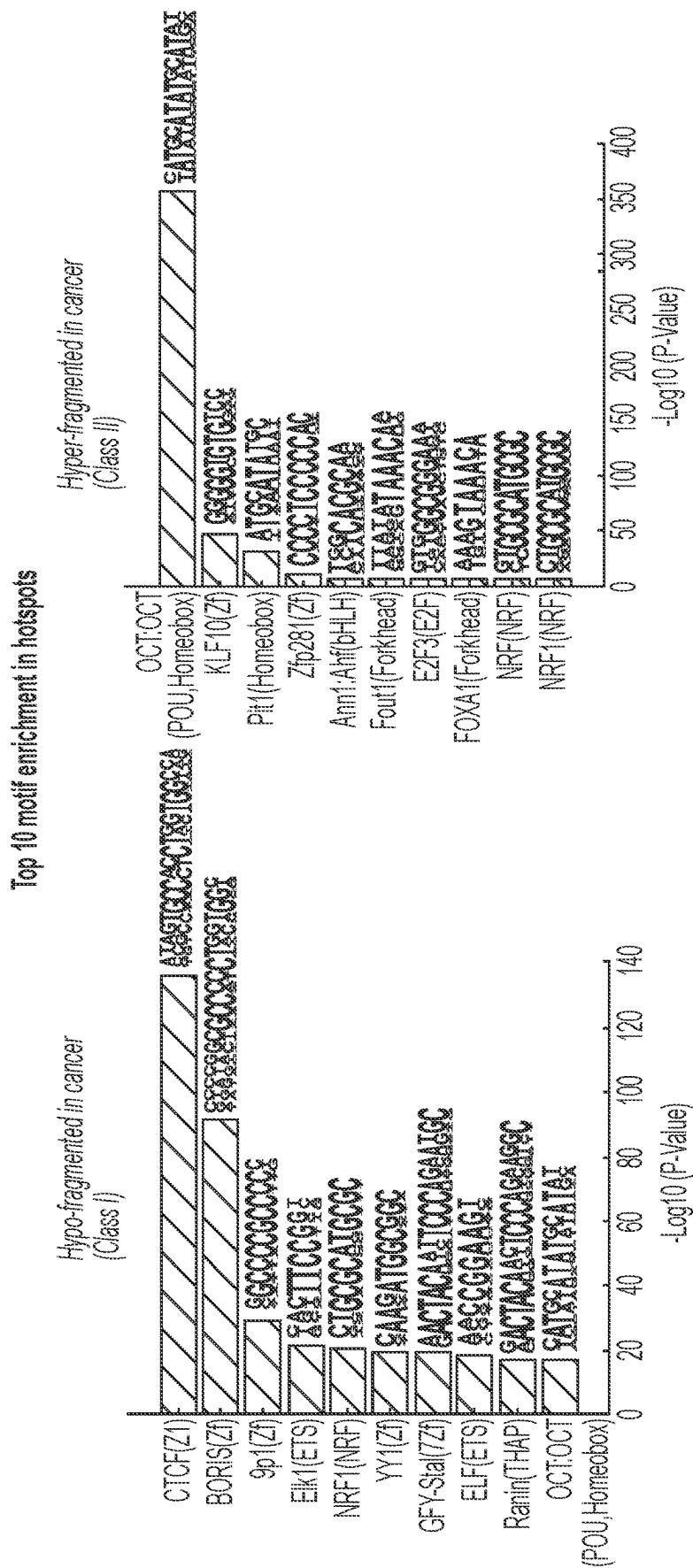


FIG. 3f

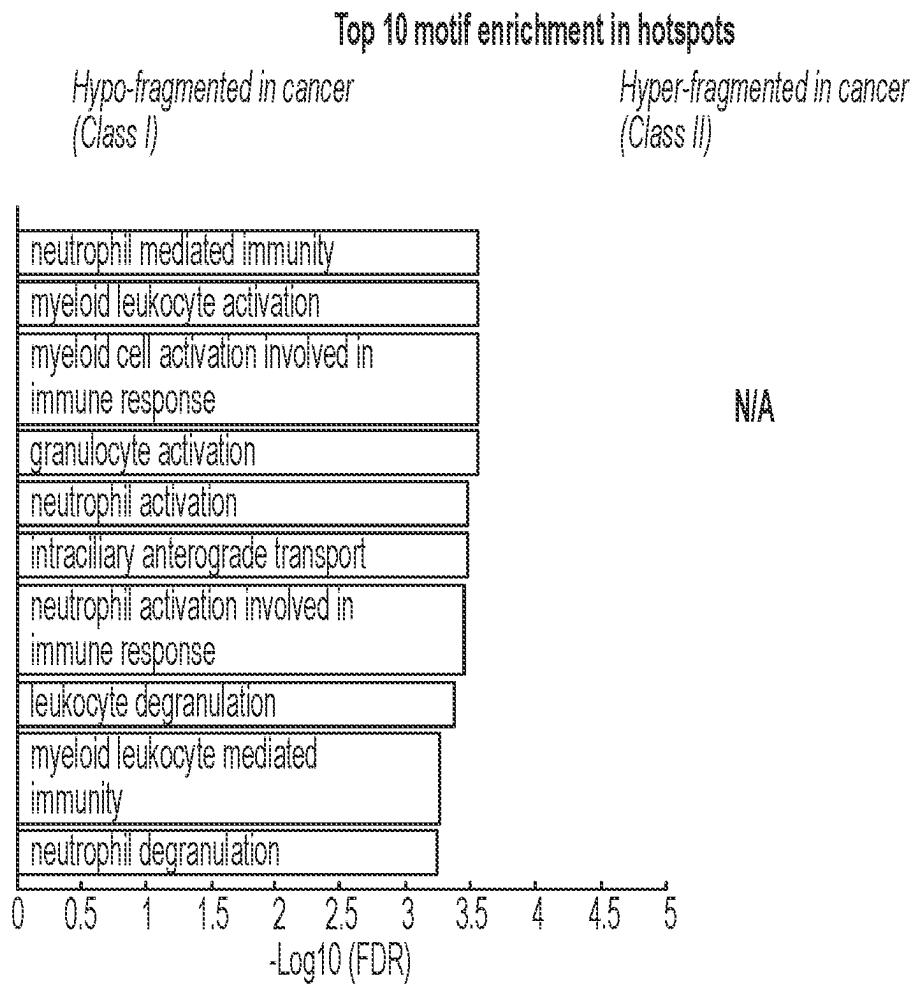


FIG. 3g

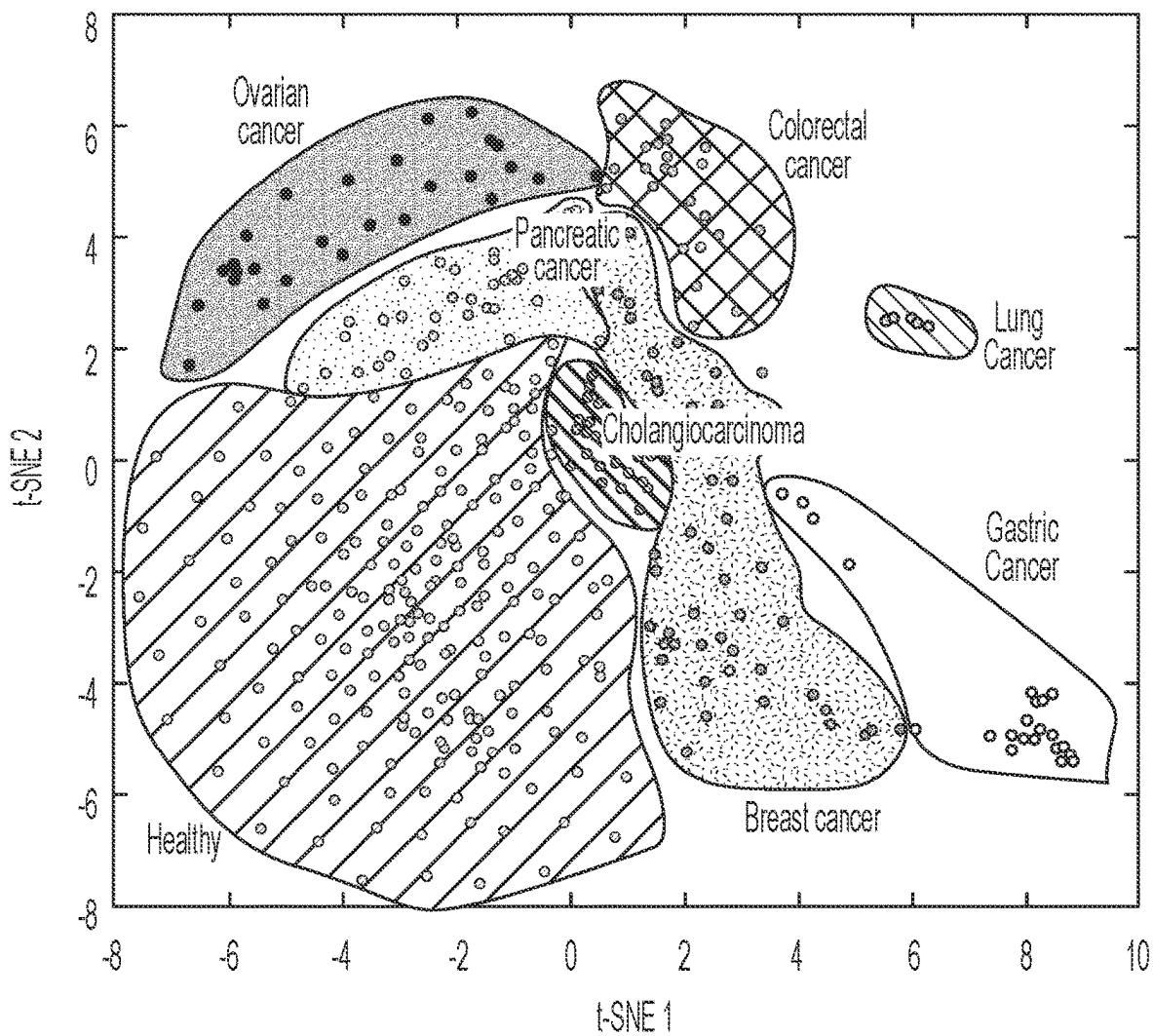


FIG. 4a

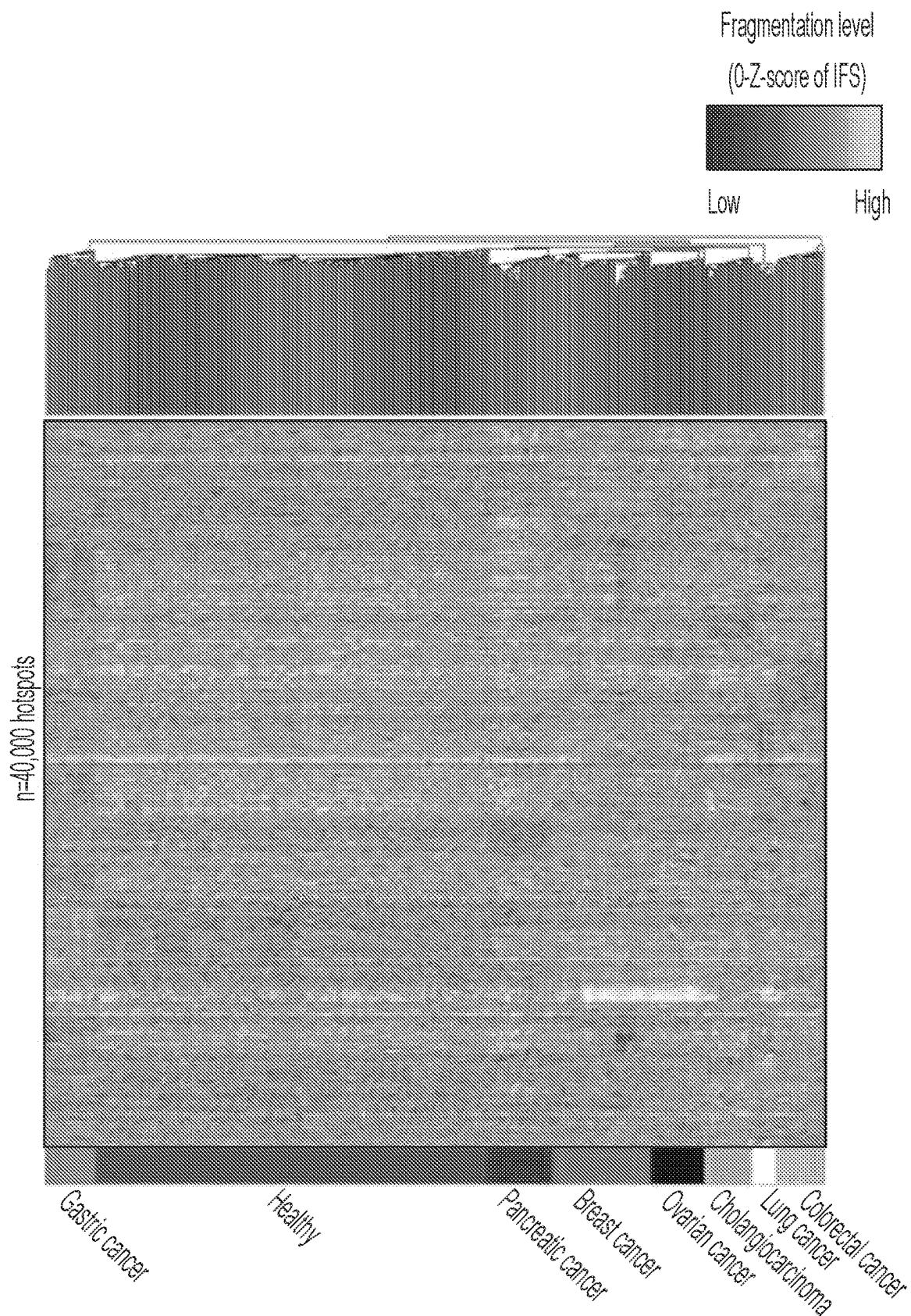


FIG. 4b

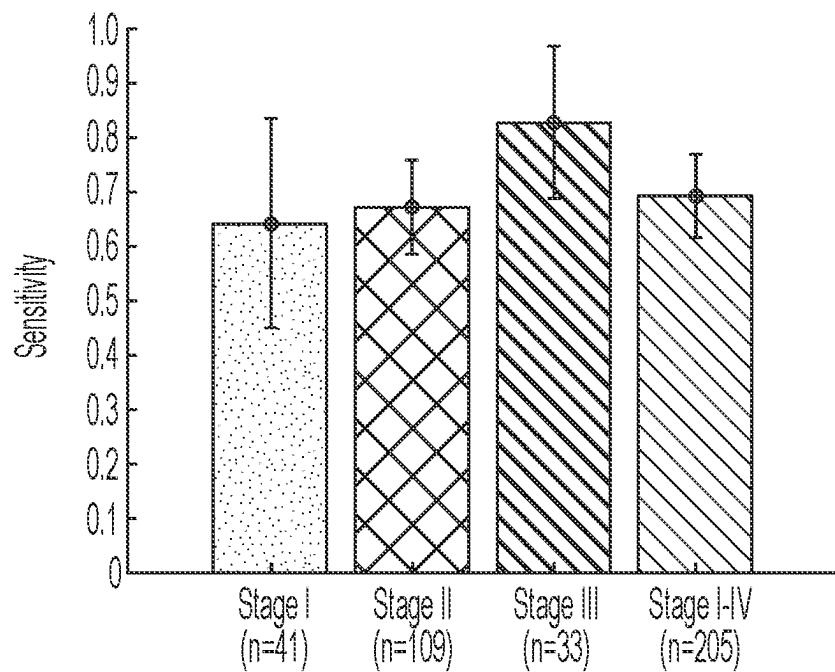


FIG. 4c

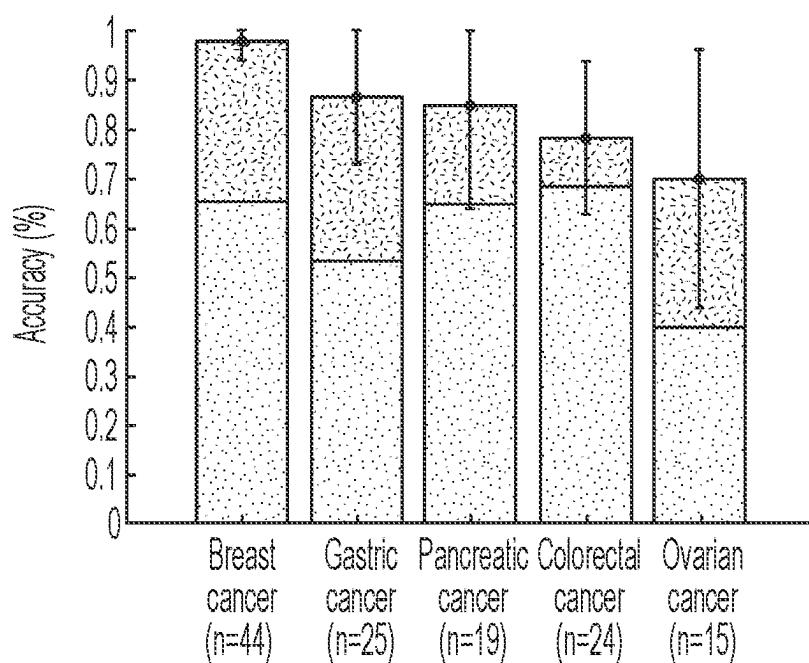


FIG. 4d

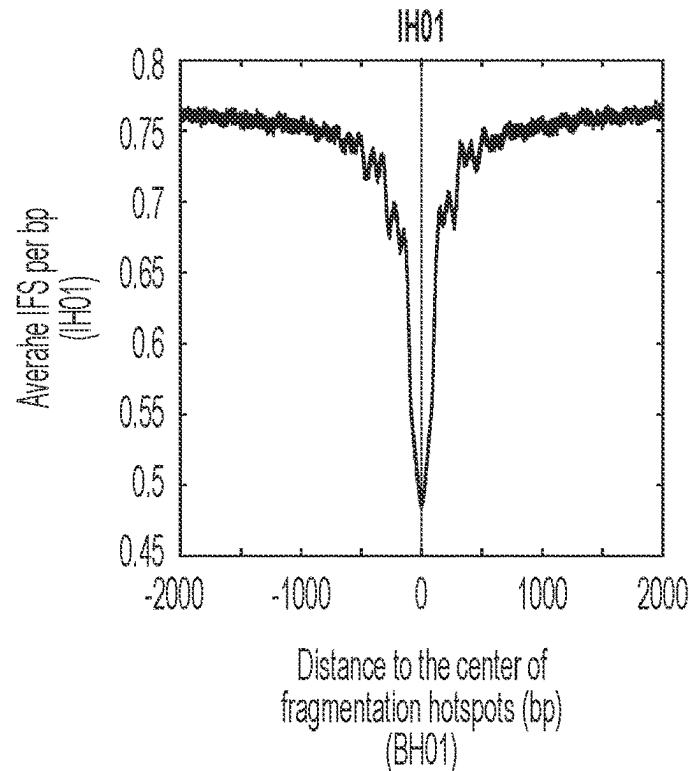


FIG. S1a

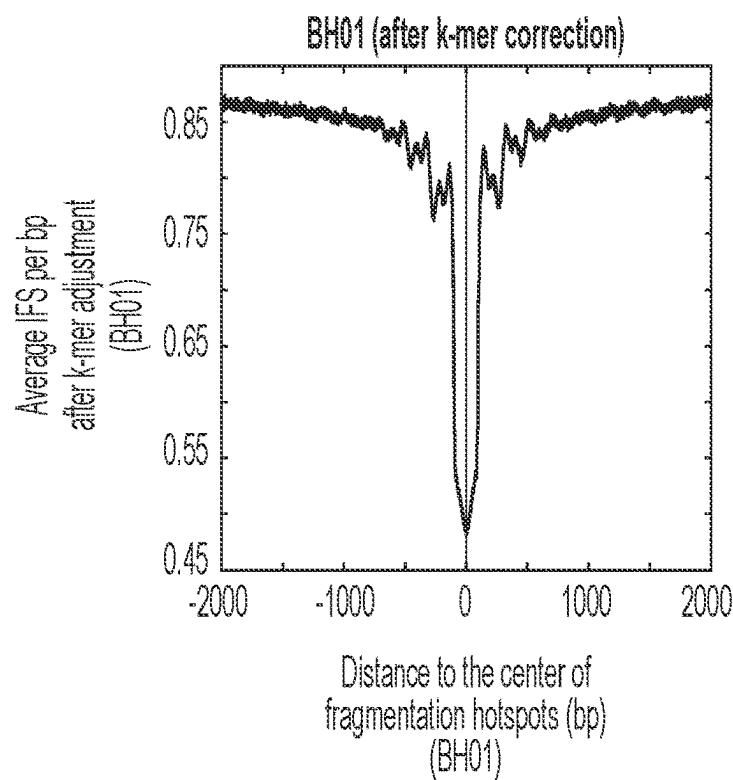
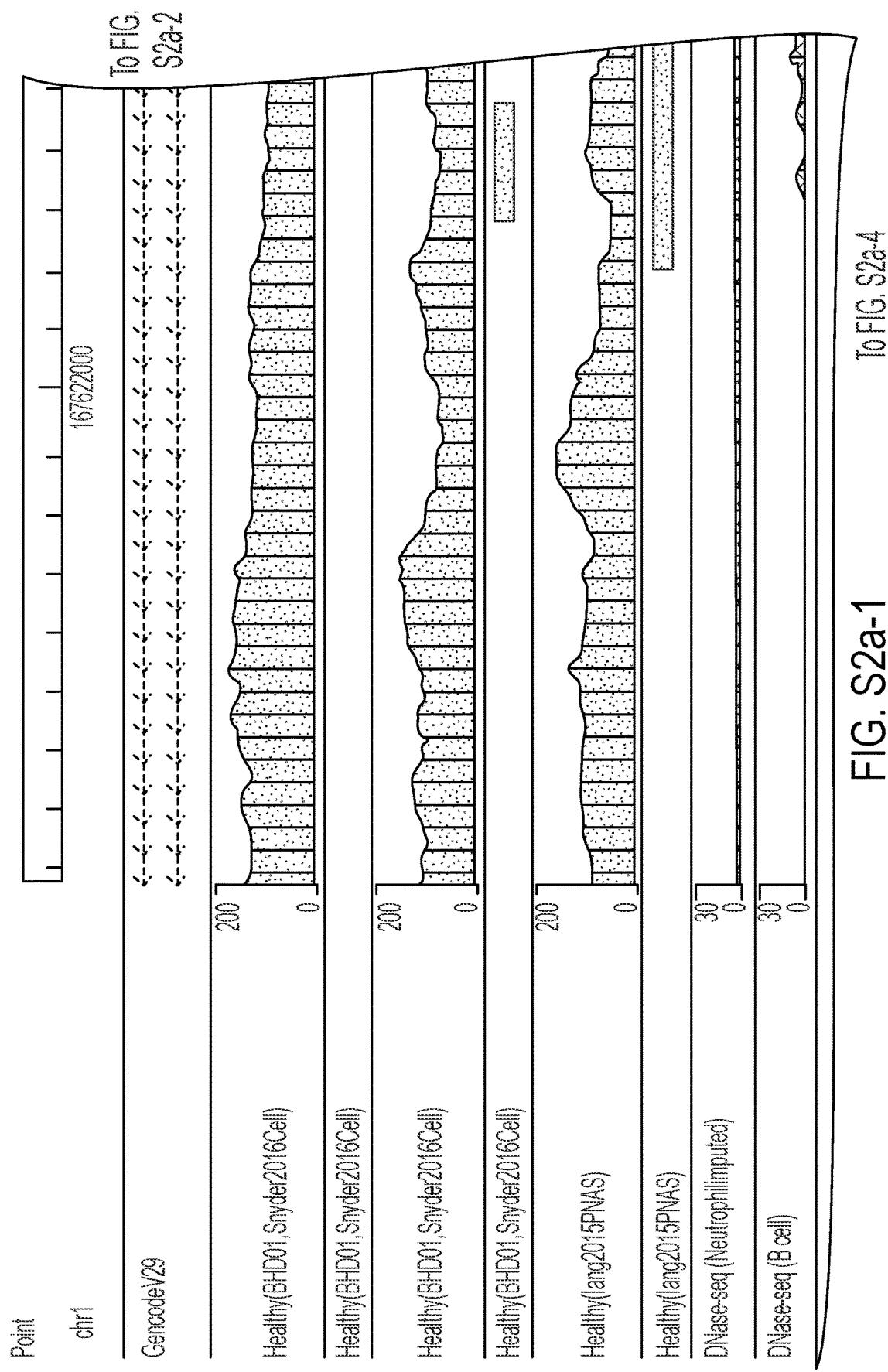
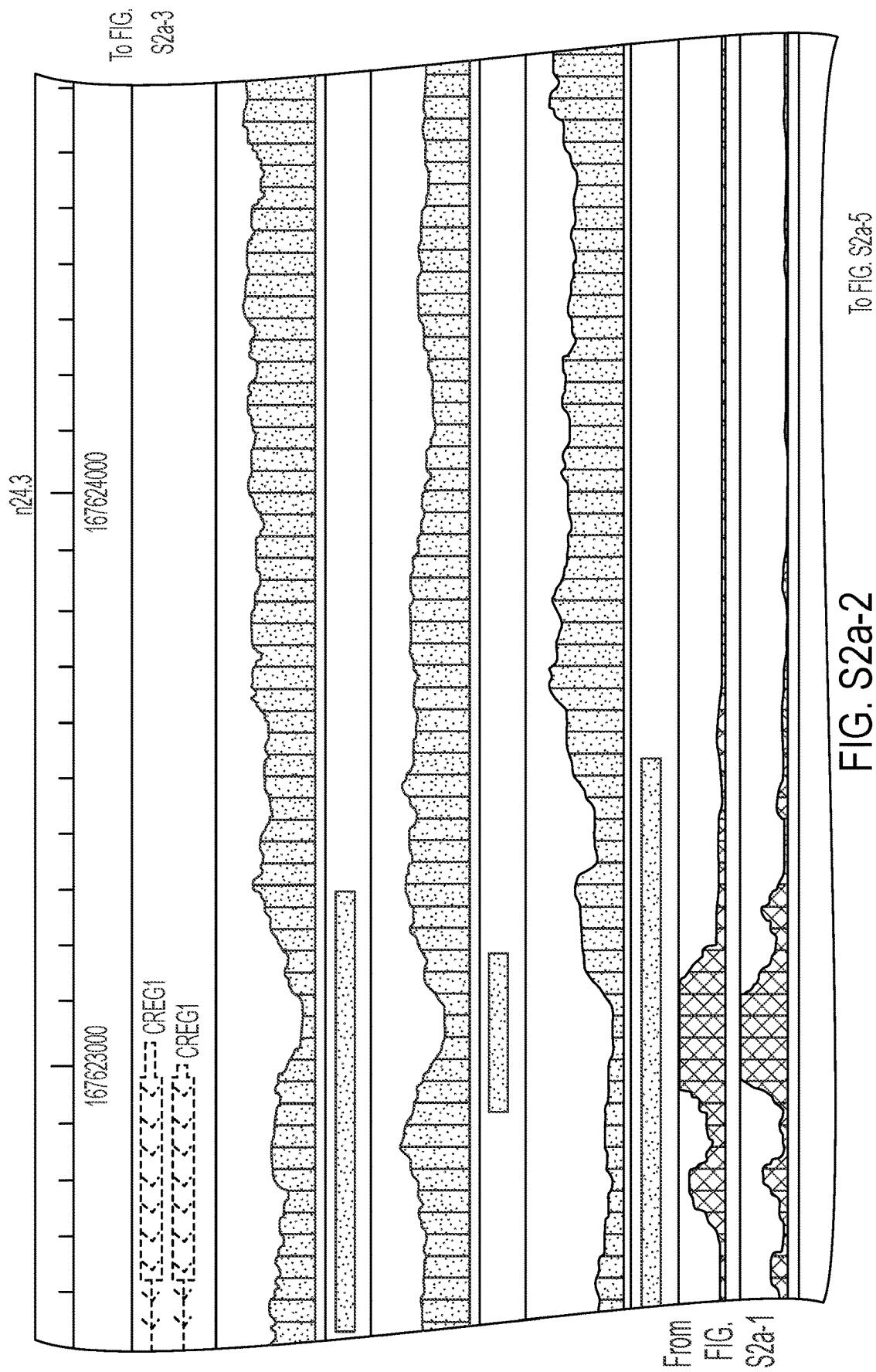


FIG. S1b





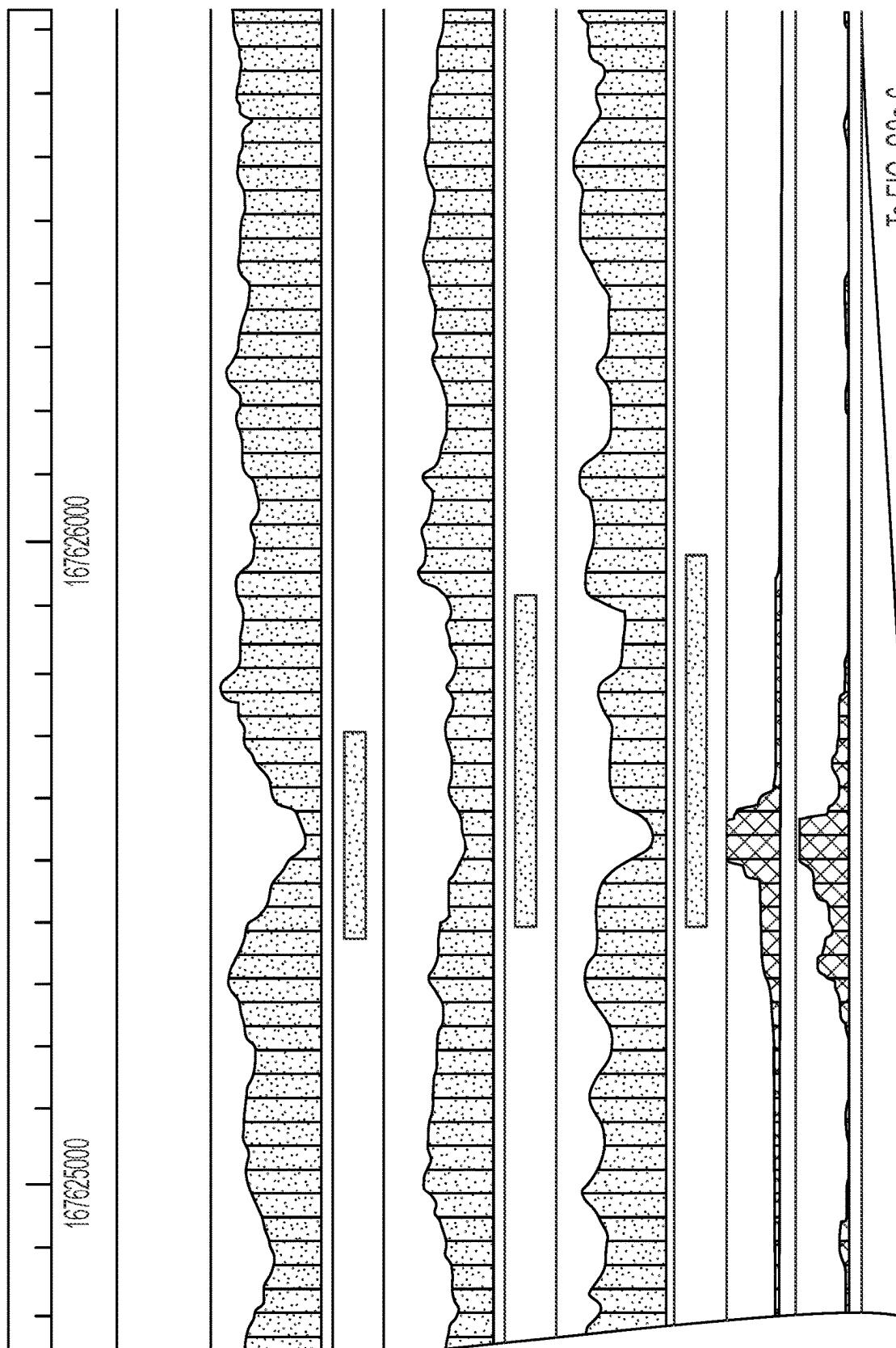
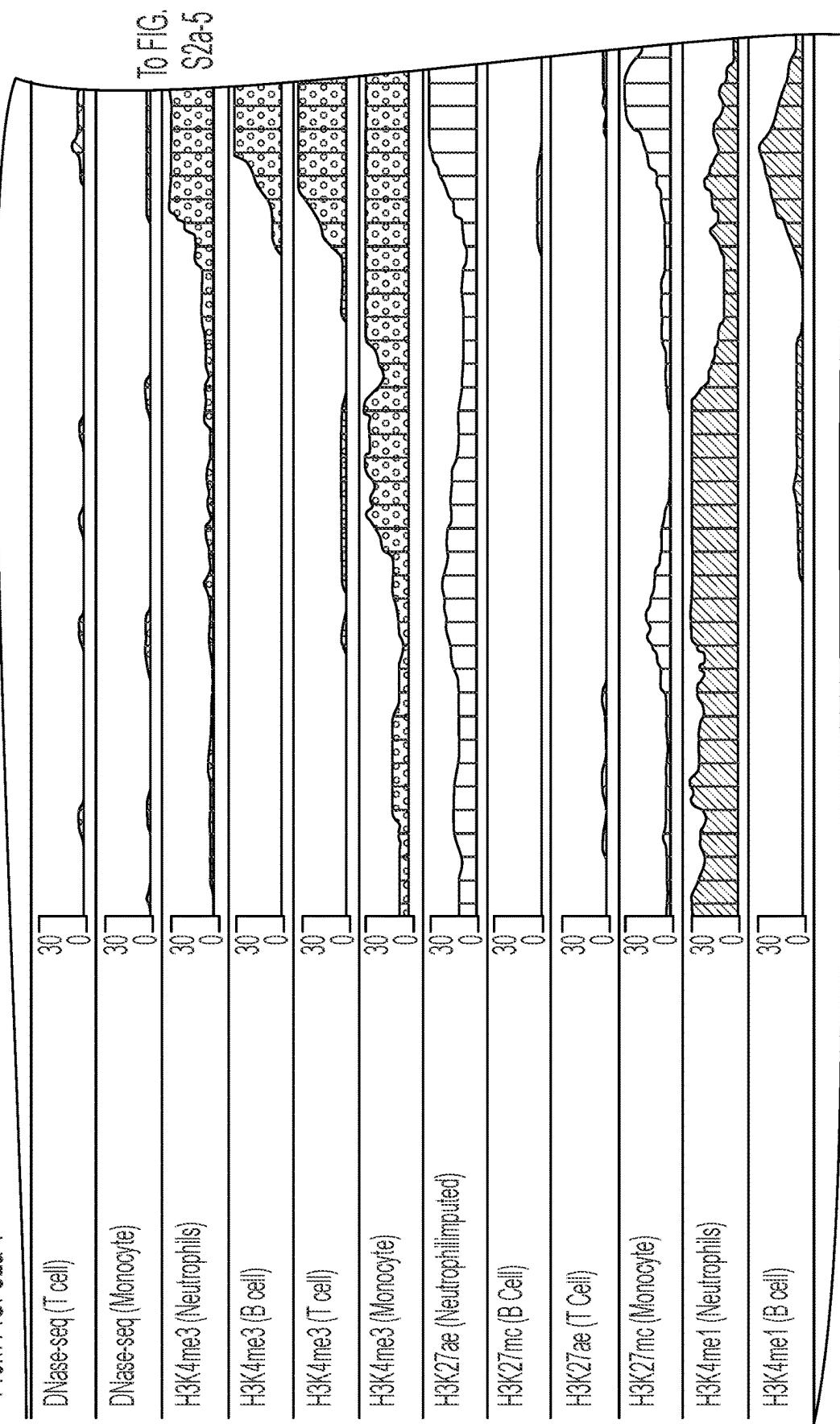


FIG. S2a-3

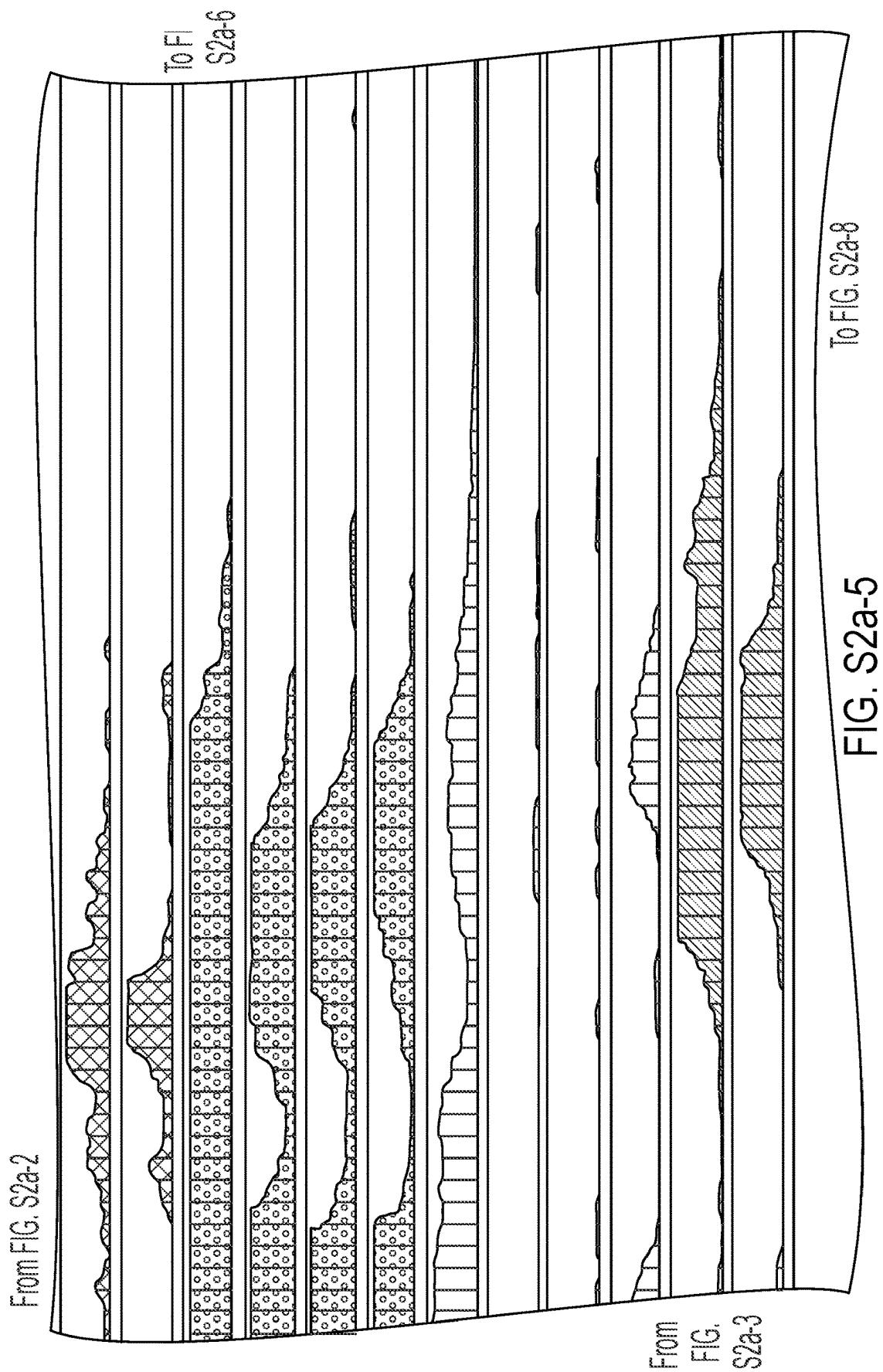
From FIG. S2a-1

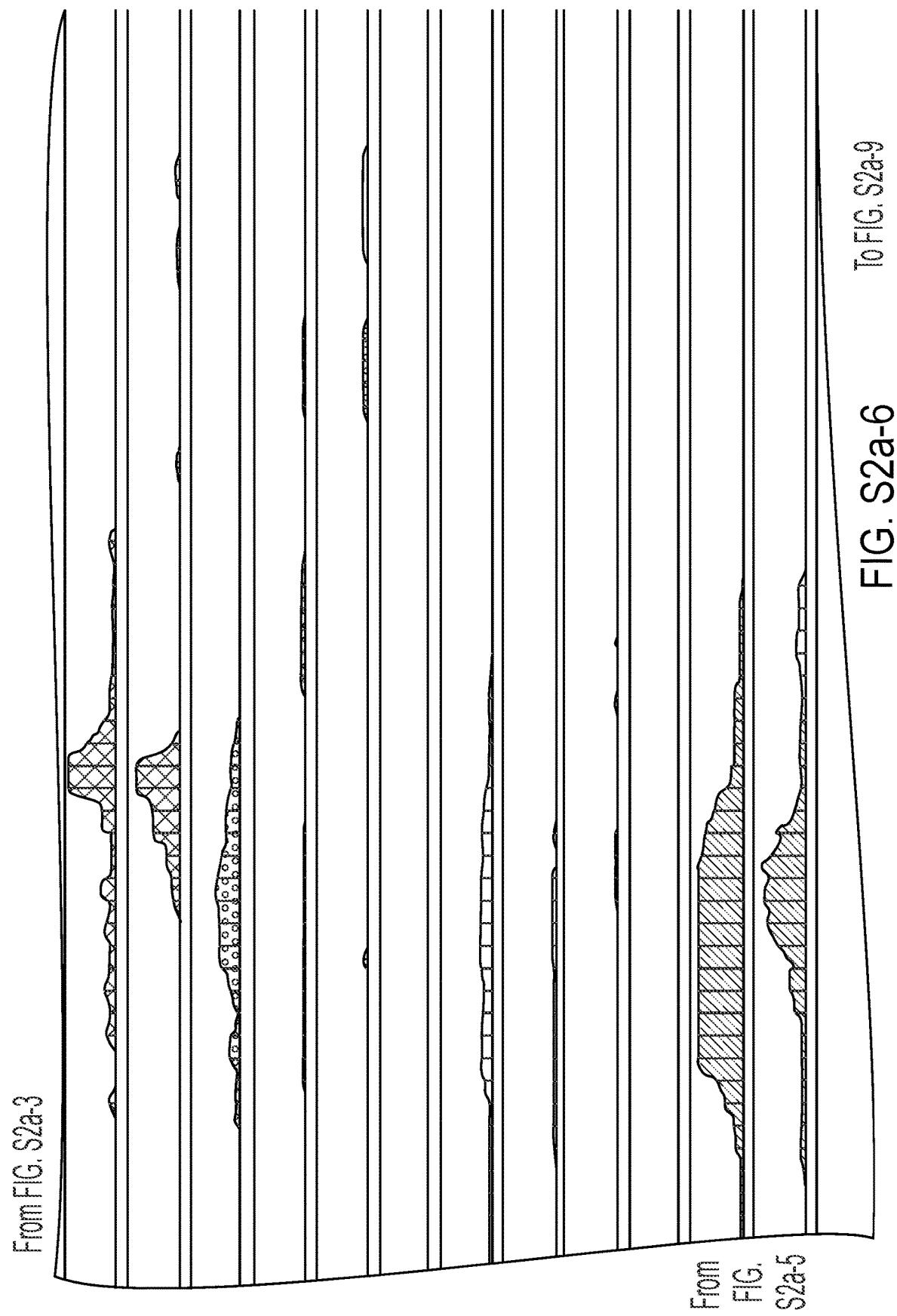


To FIG.
S2a-5

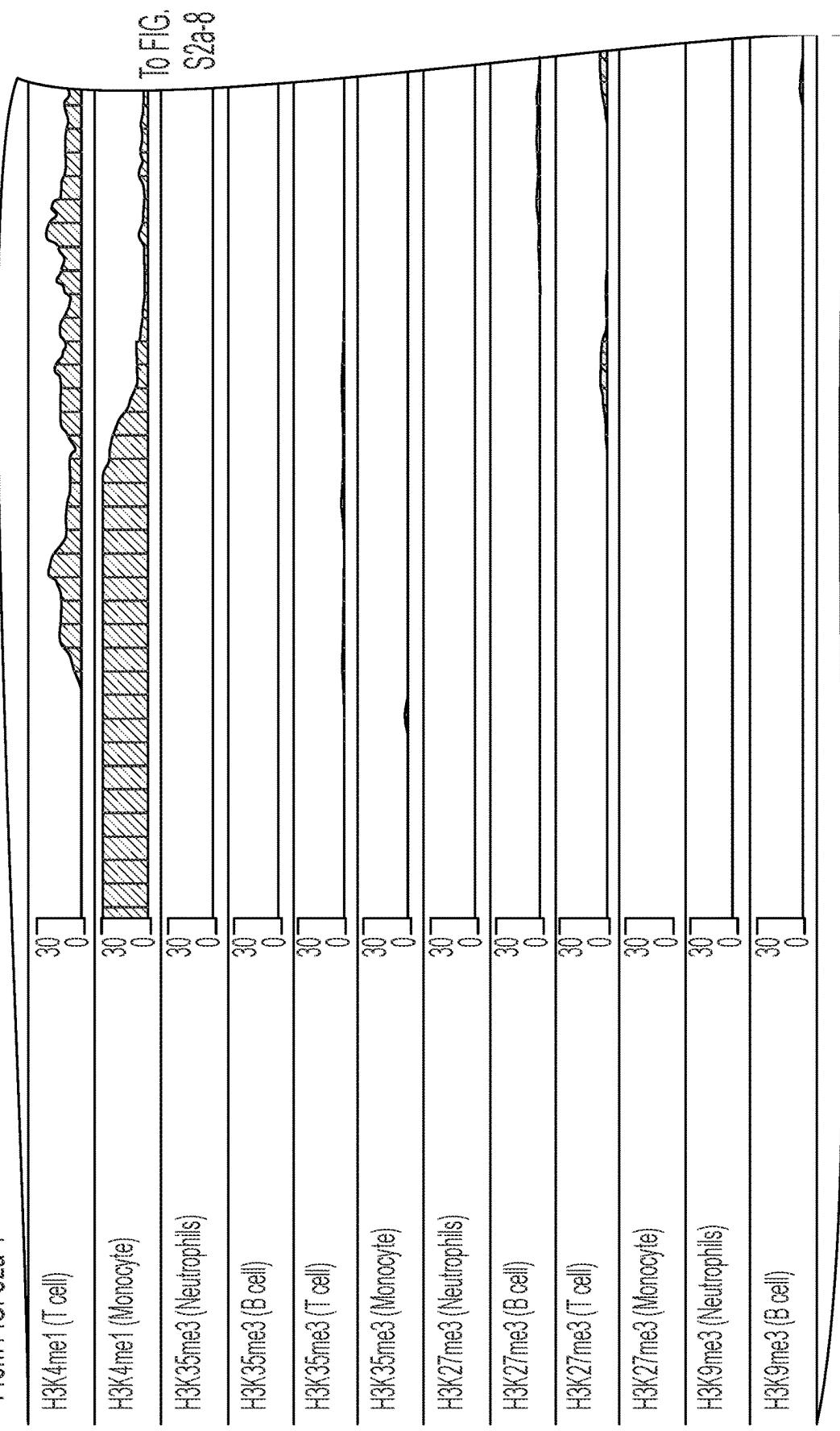
To FIG. S2a-7

FIG. S2a-4

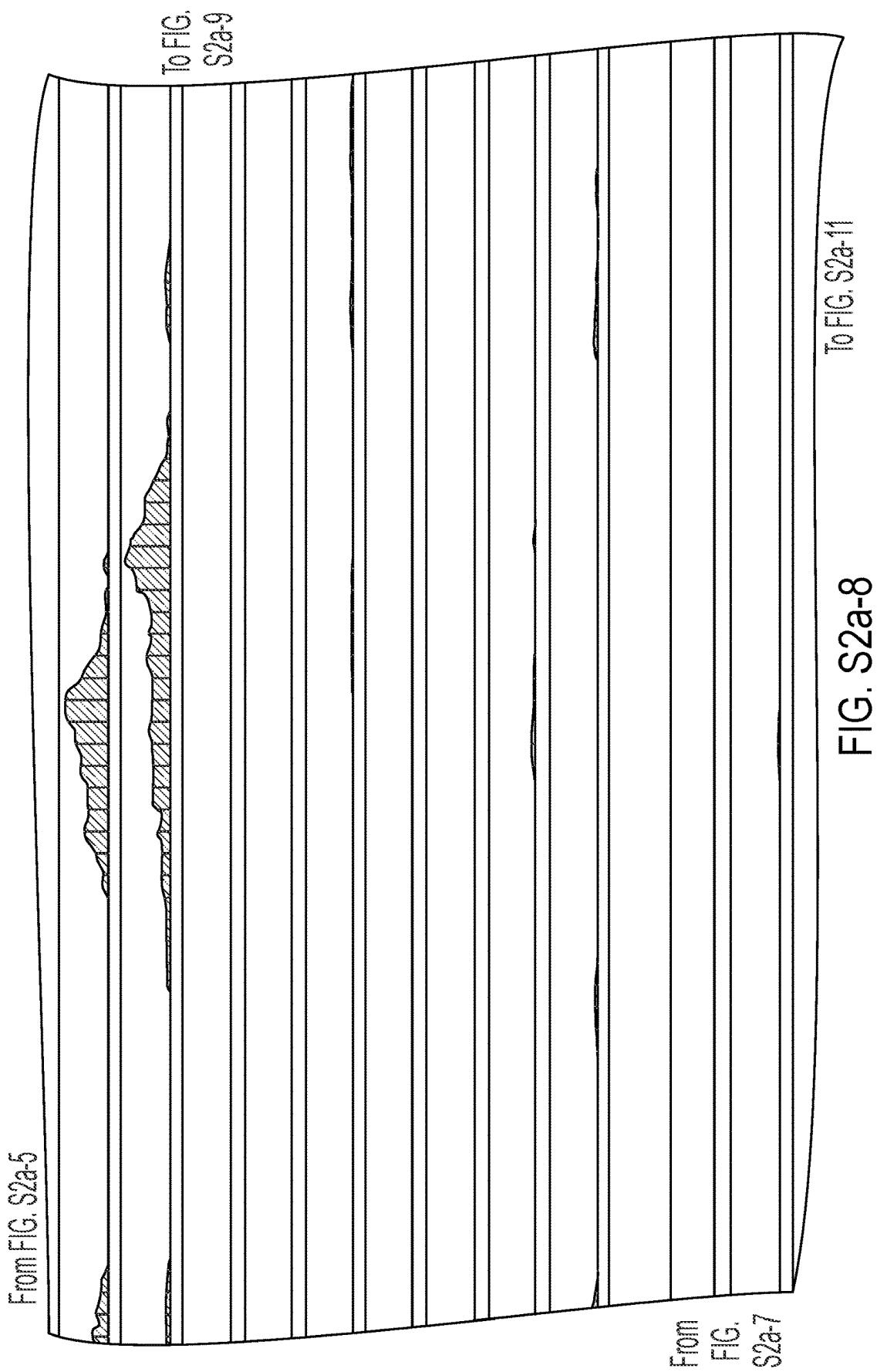


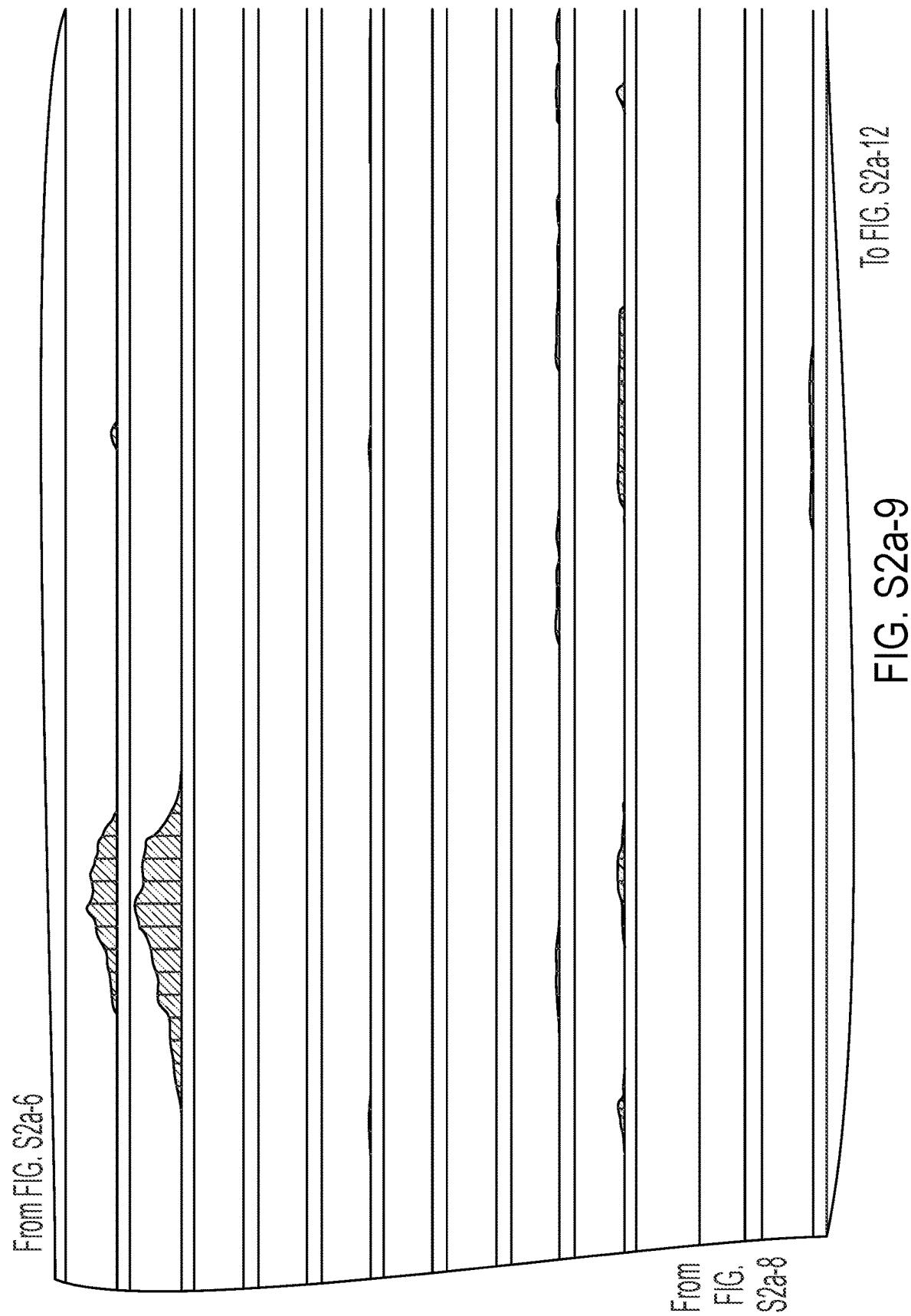


From FIG. S2a-4



To FIG. S2a-7
To FIG. S2a-10





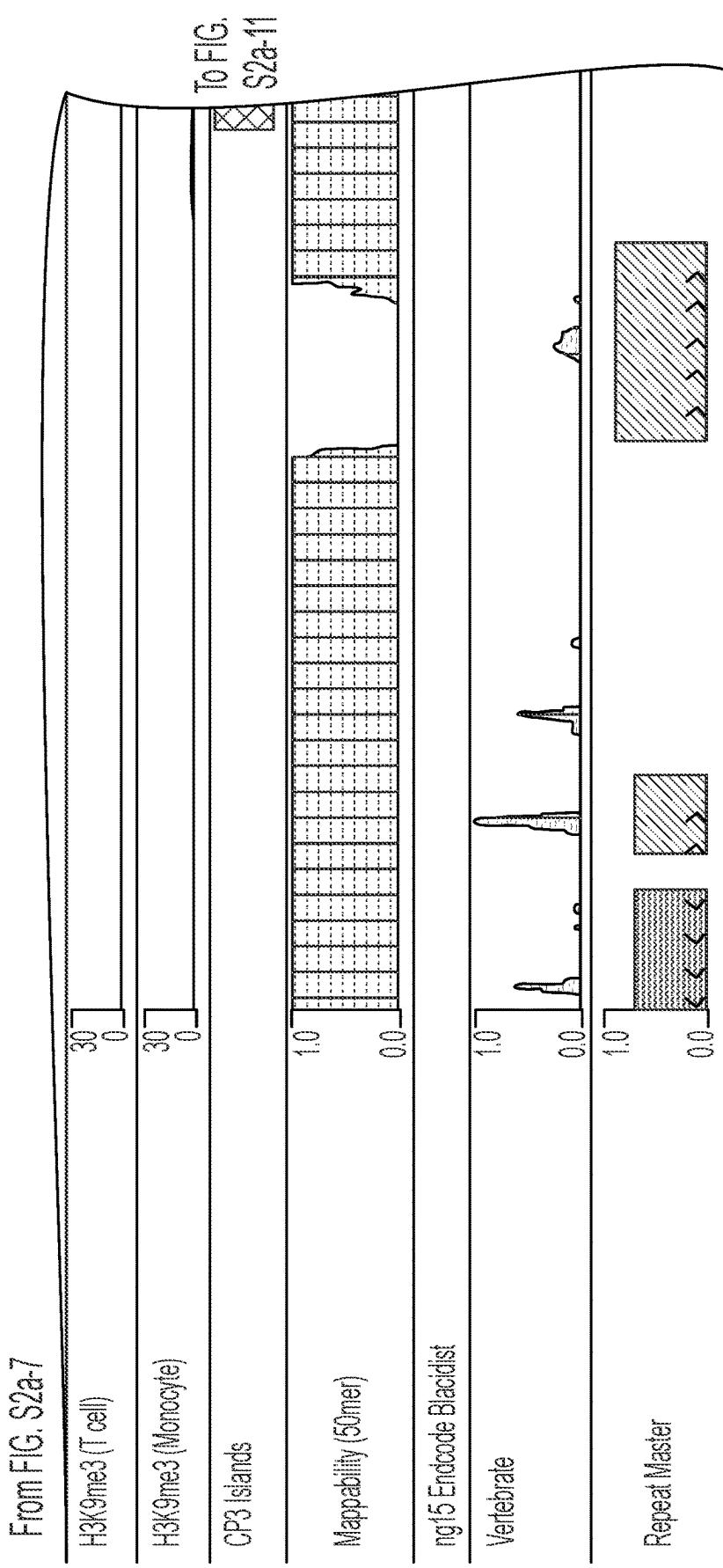


FIG. S2a-10

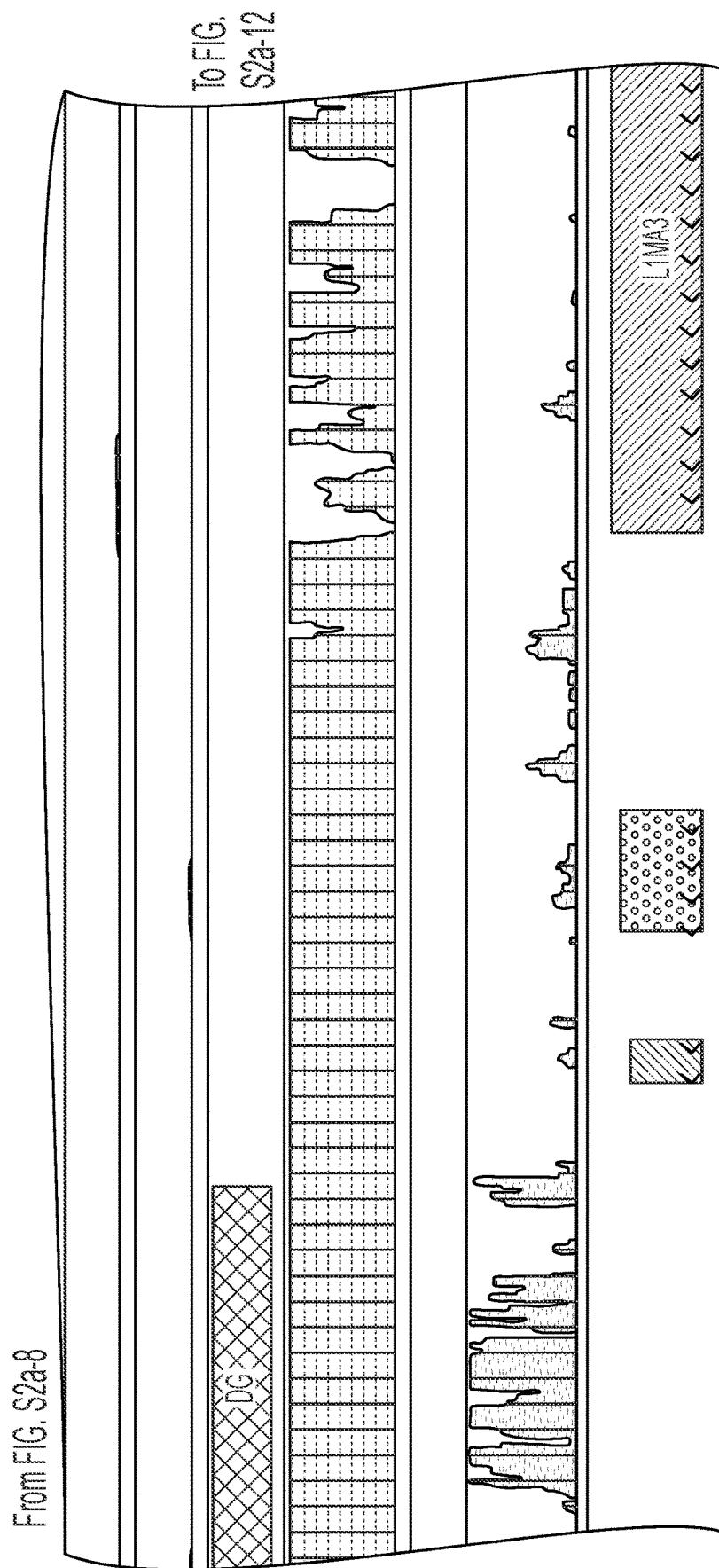


FIG. S2a-4

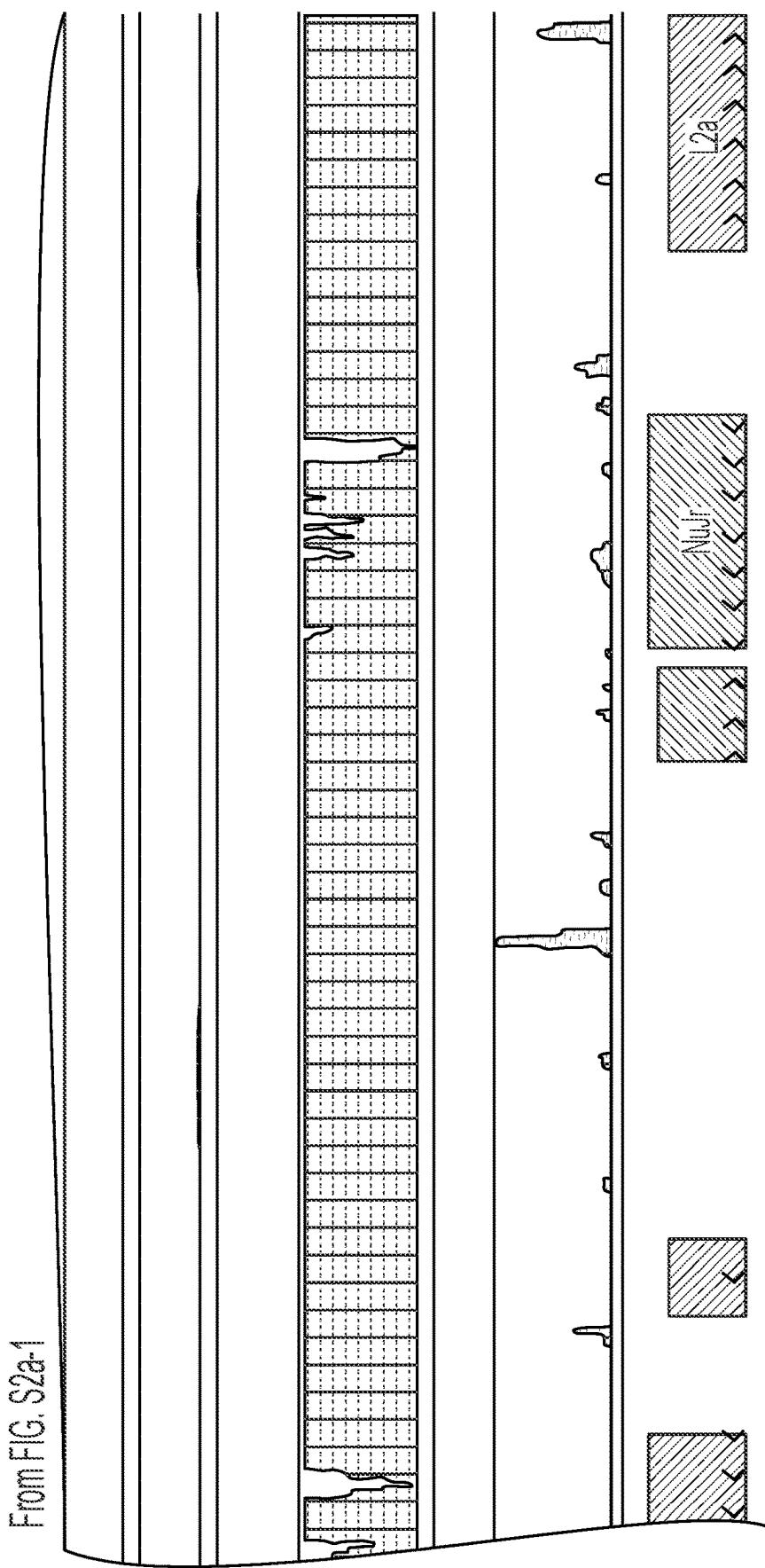


FIG. S2a-12

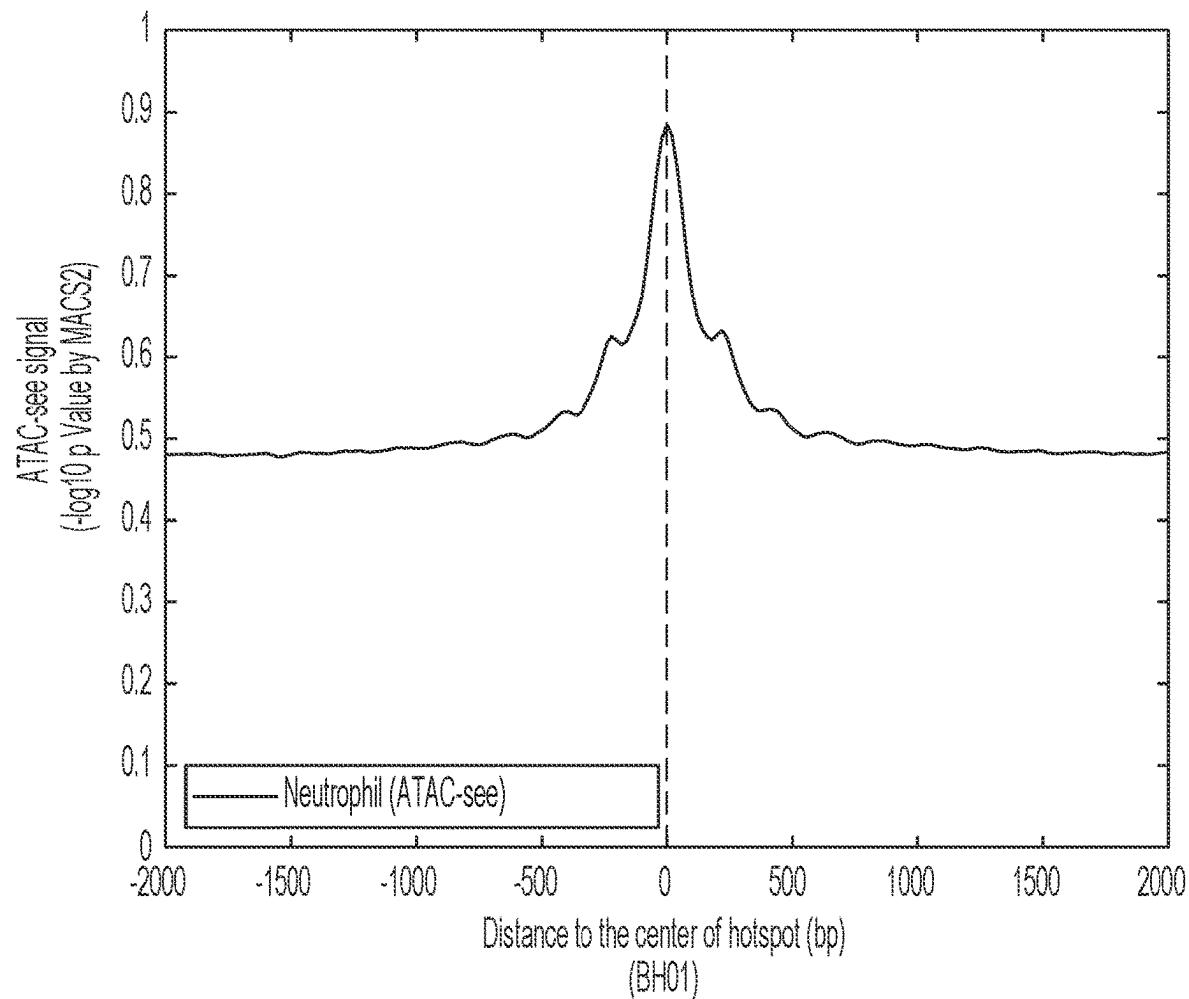


FIG. S3

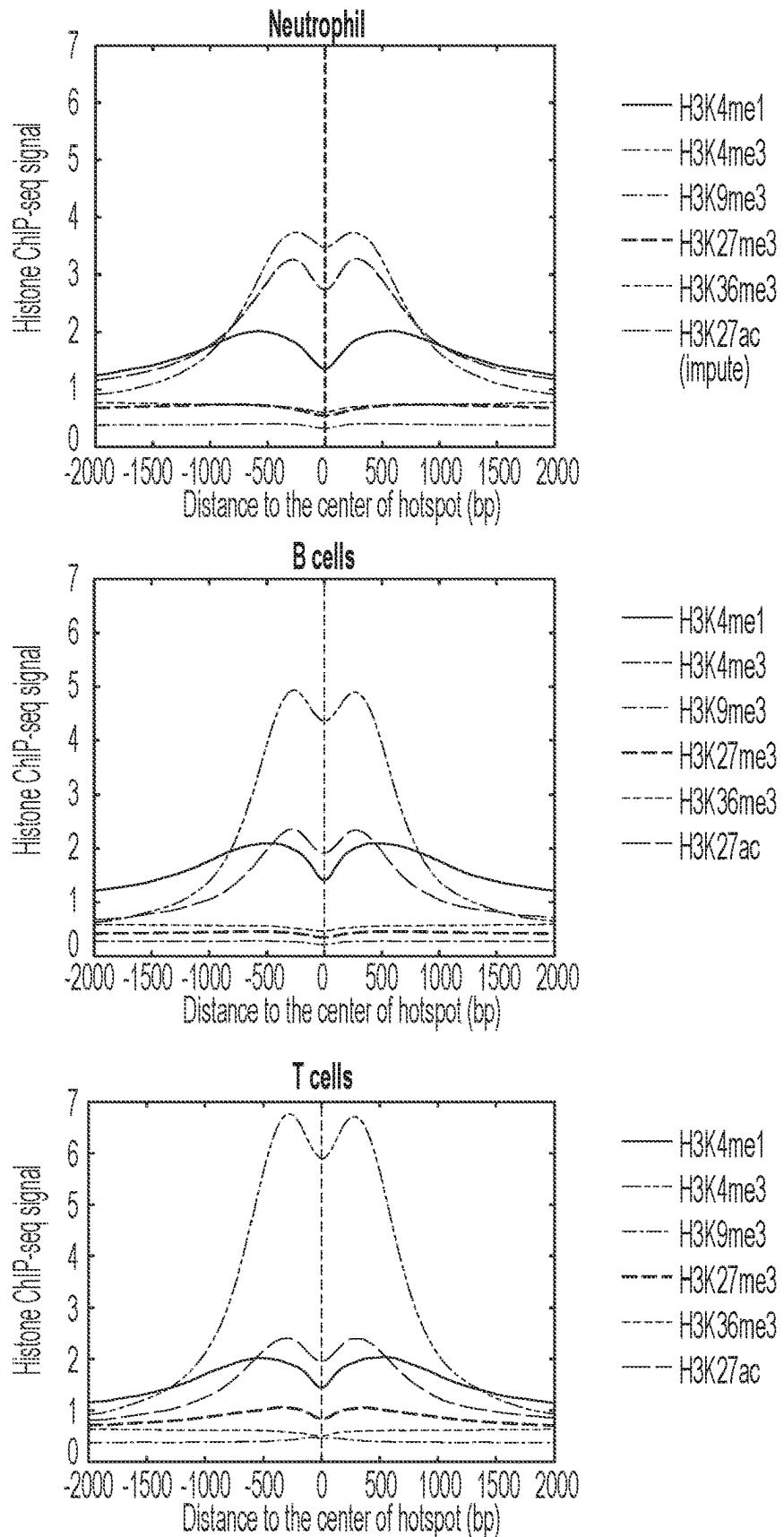


FIG. S4a

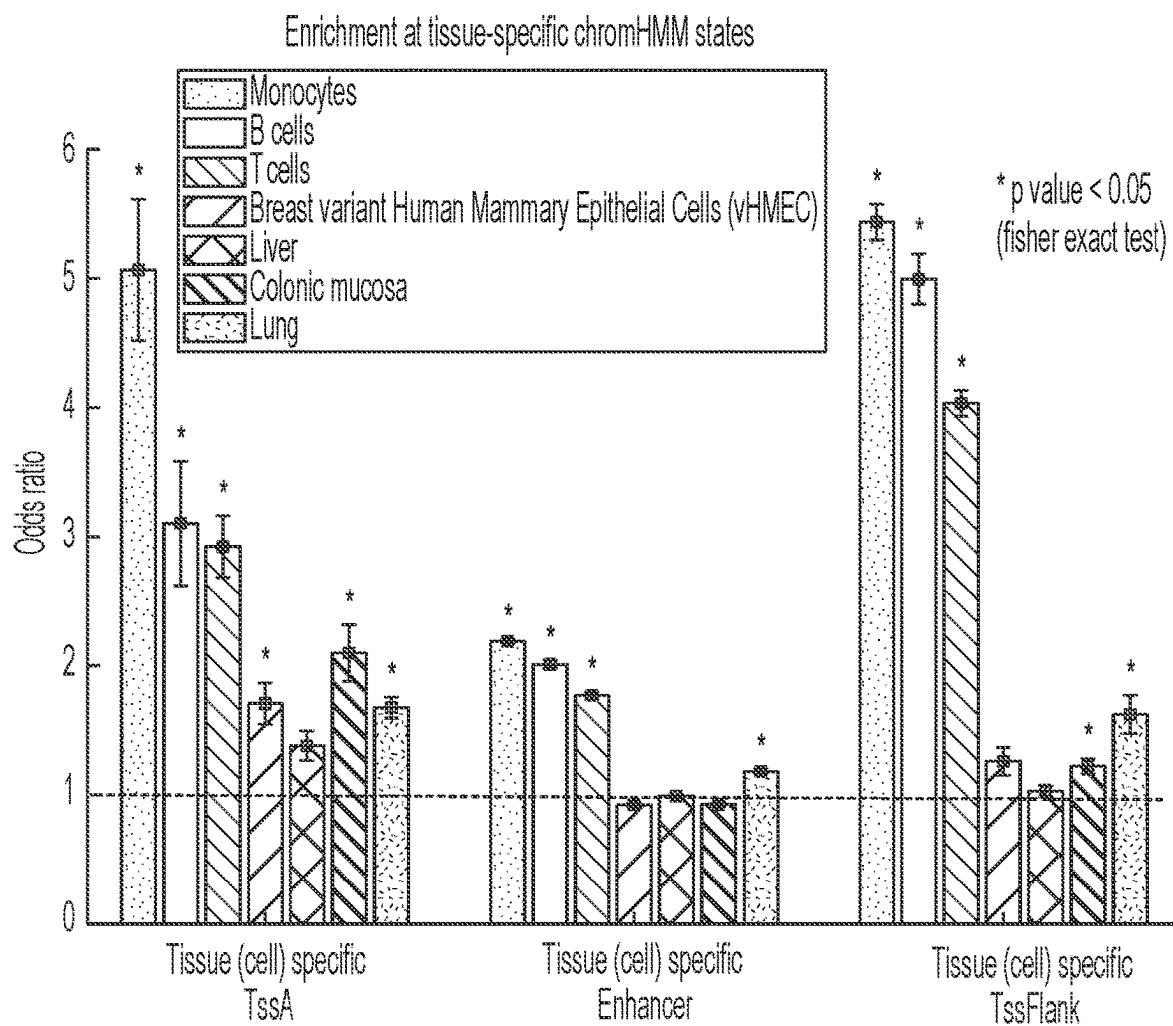


FIG. S4b

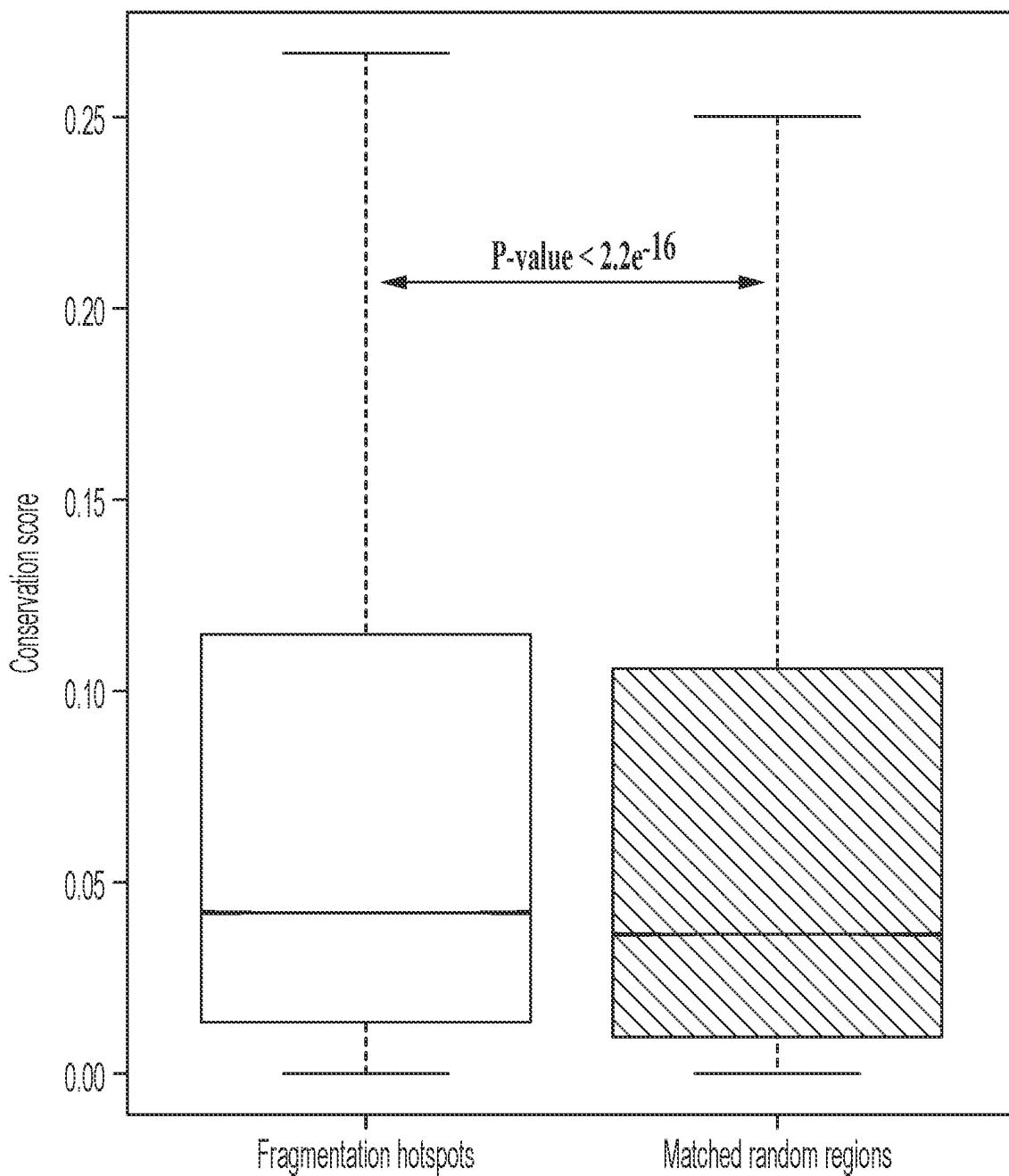


FIG. S5

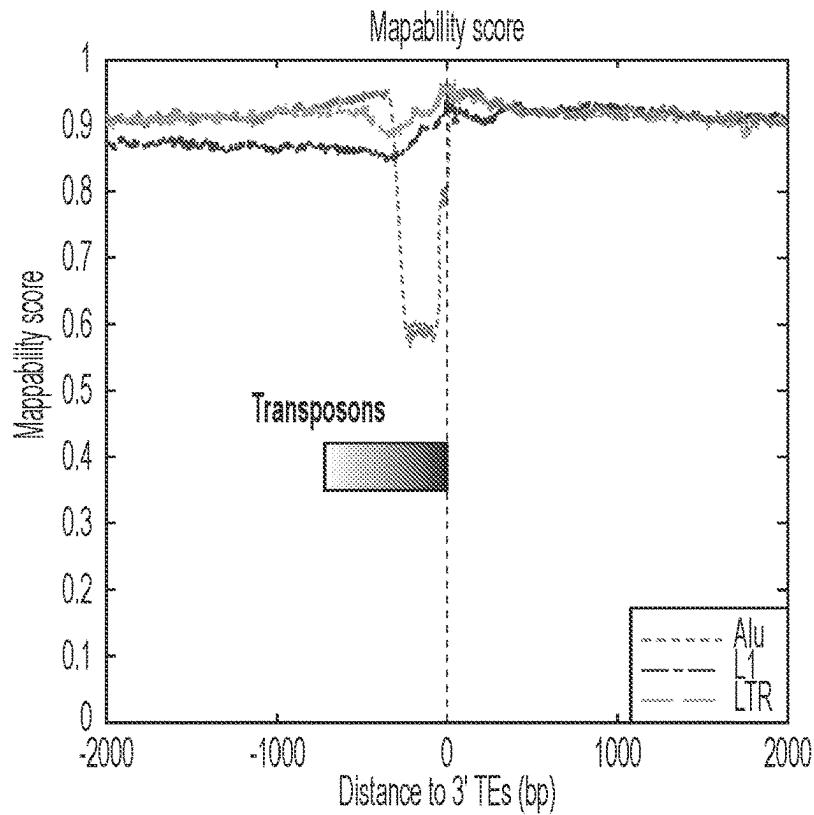


FIG. S6a

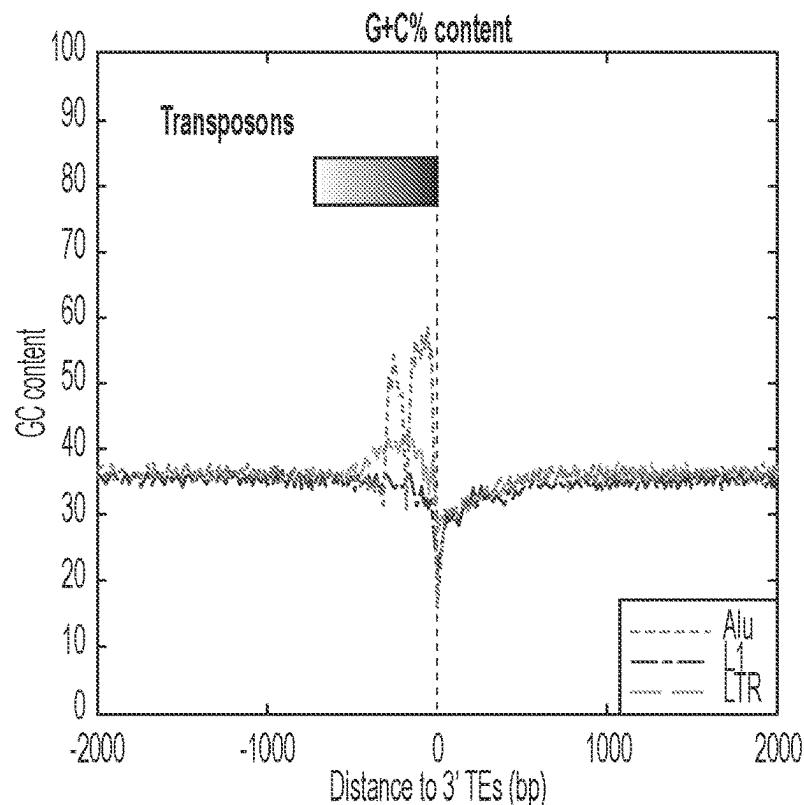


FIG. S6b

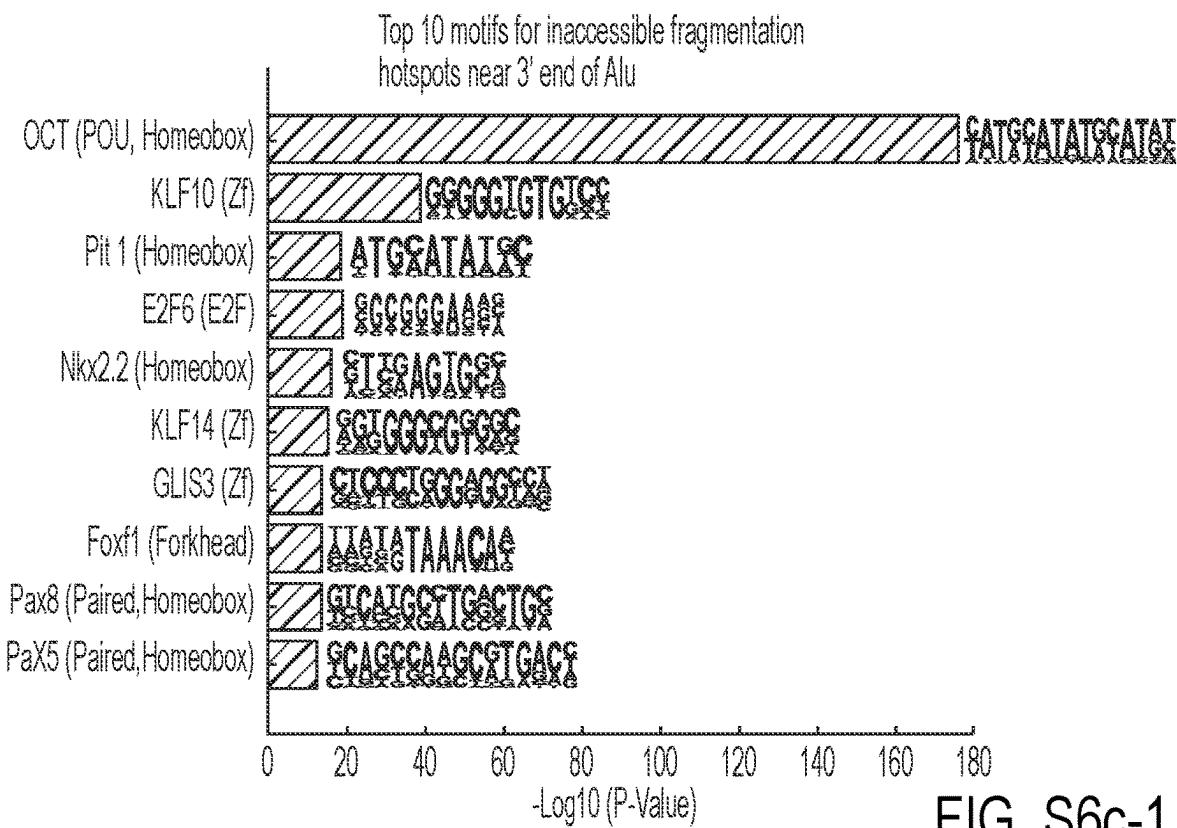


FIG. S6c-1

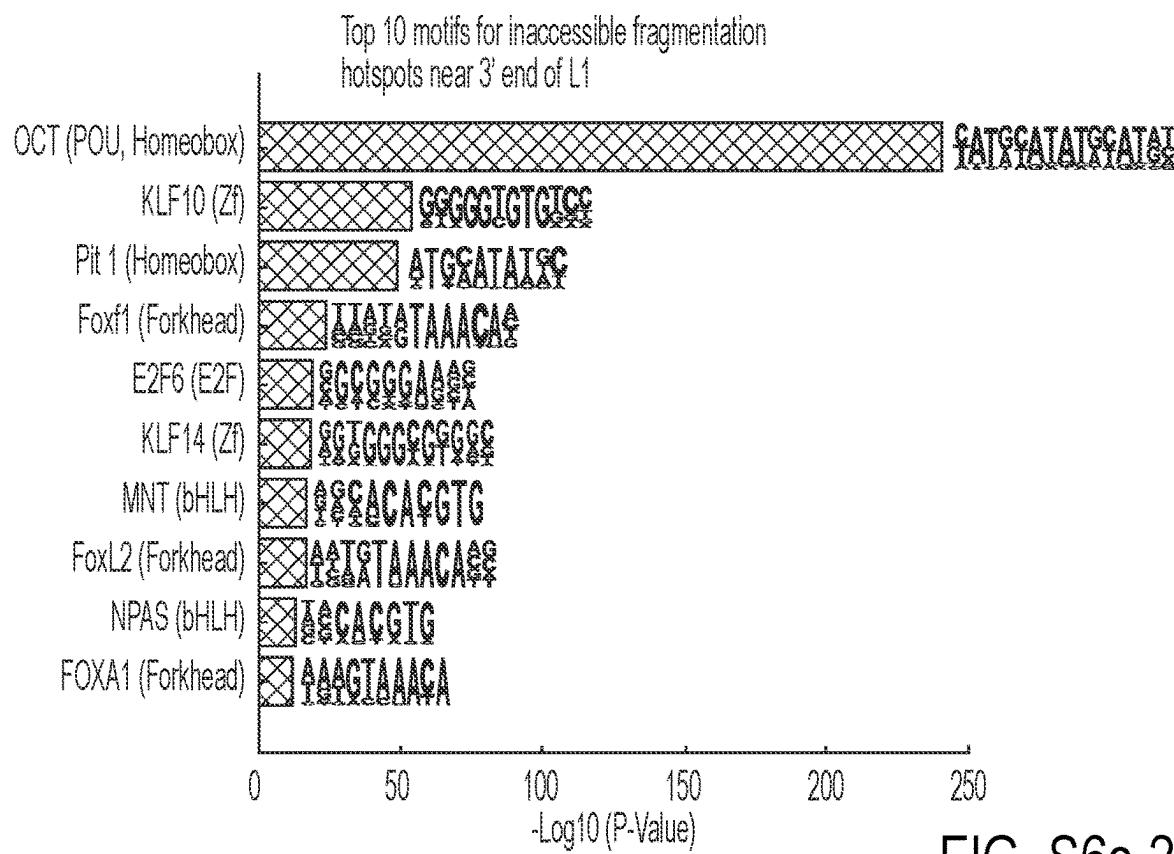


FIG. S6c-2

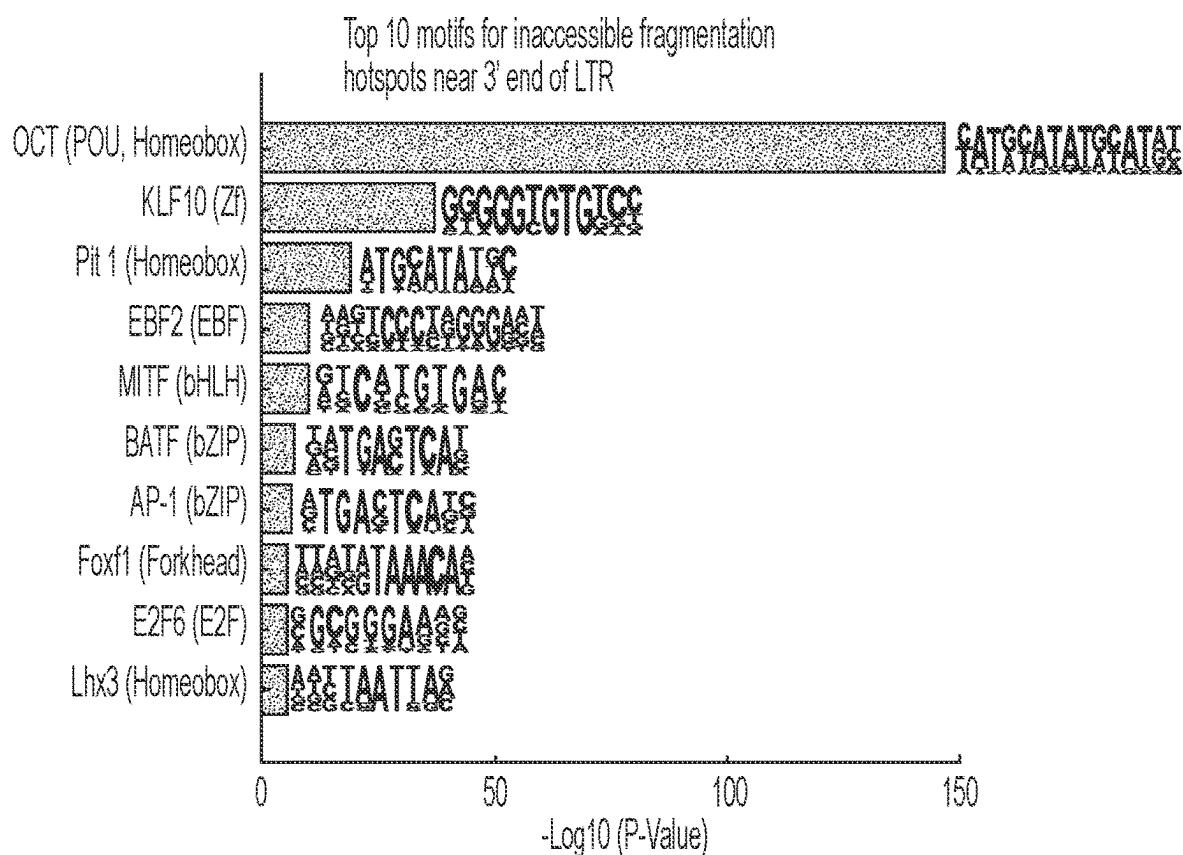


FIG. S6c-3

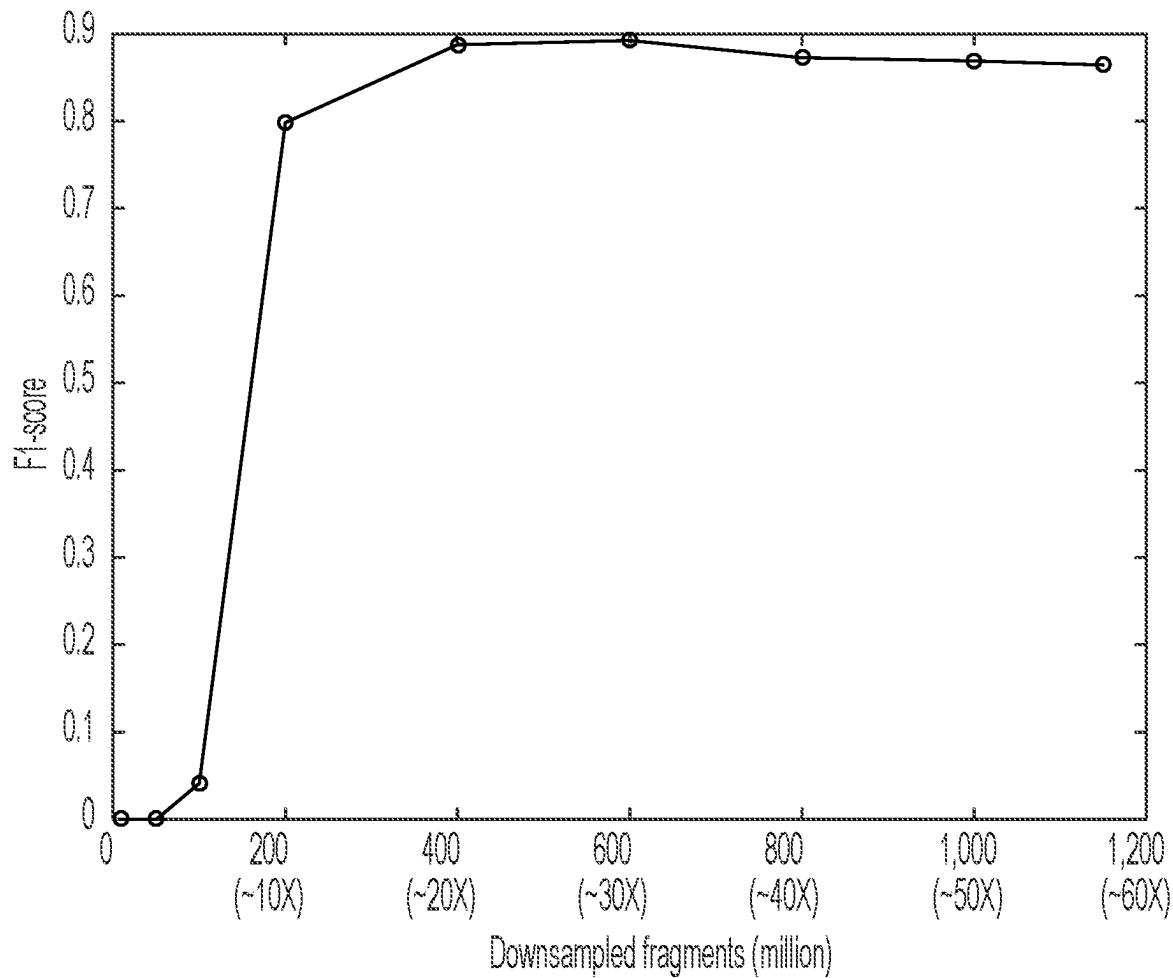


FIG. S7

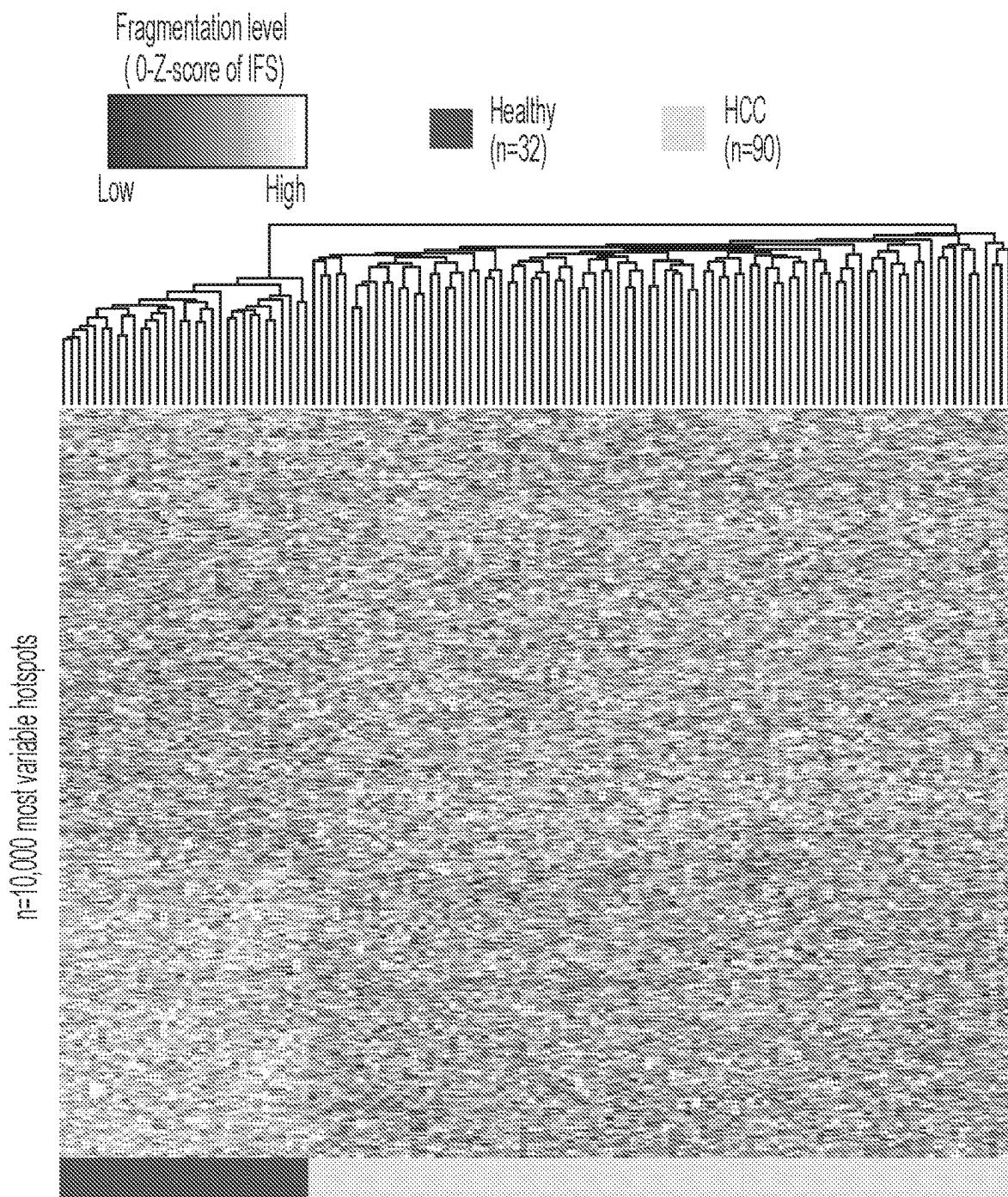


FIG. S8

Top 10,000 most variable hotspots
(distance metrics: euclidean)

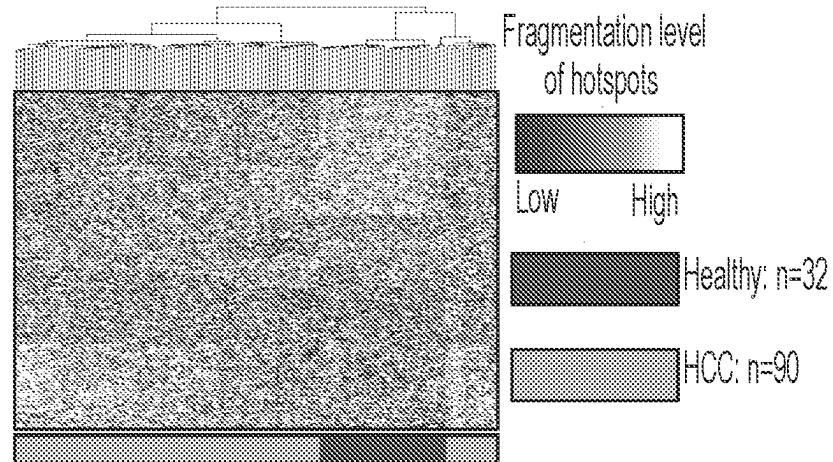


FIG. S9a

Top 20,000 most variable hotspots
(distance metrics: spearman)

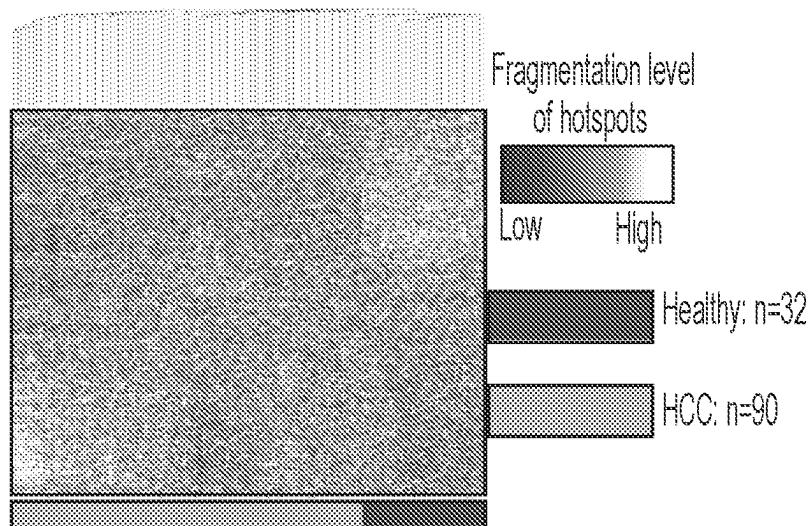


FIG. S9b

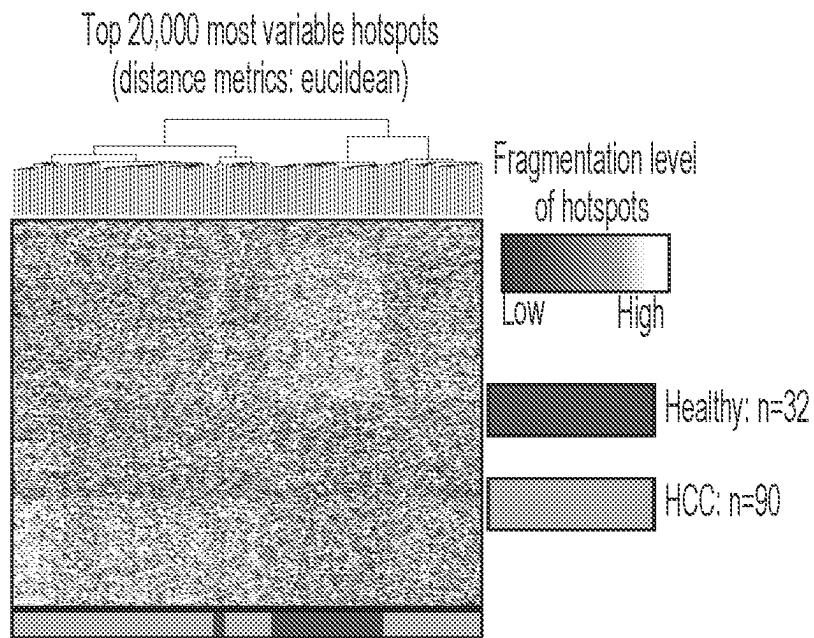


FIG. S9c

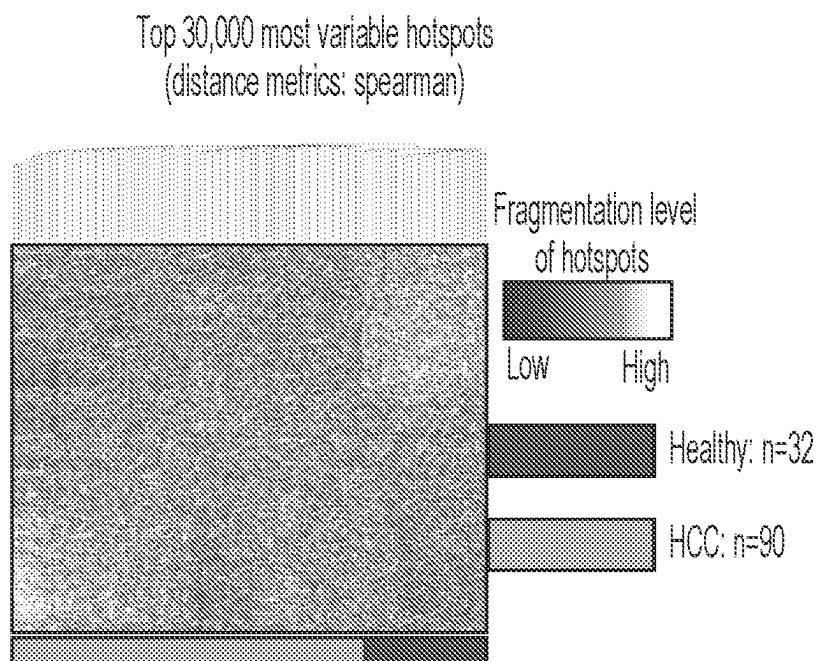


FIG. S9d

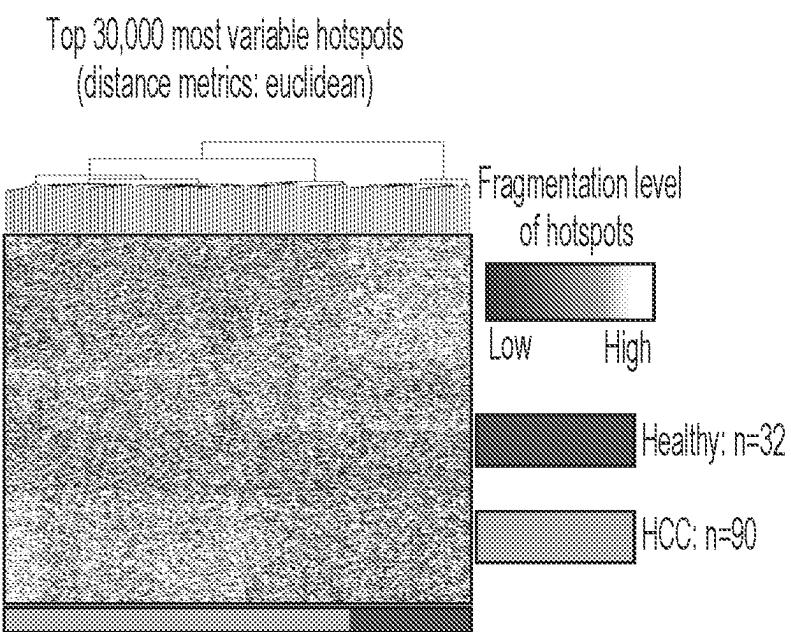


FIG. S9e

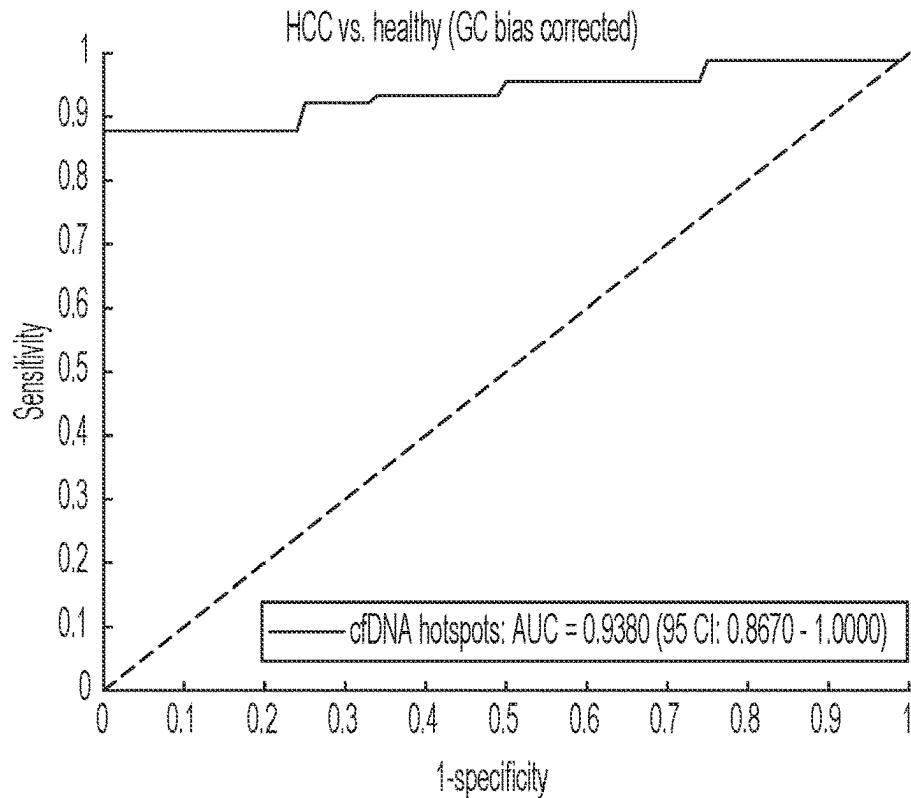


FIG. S10a

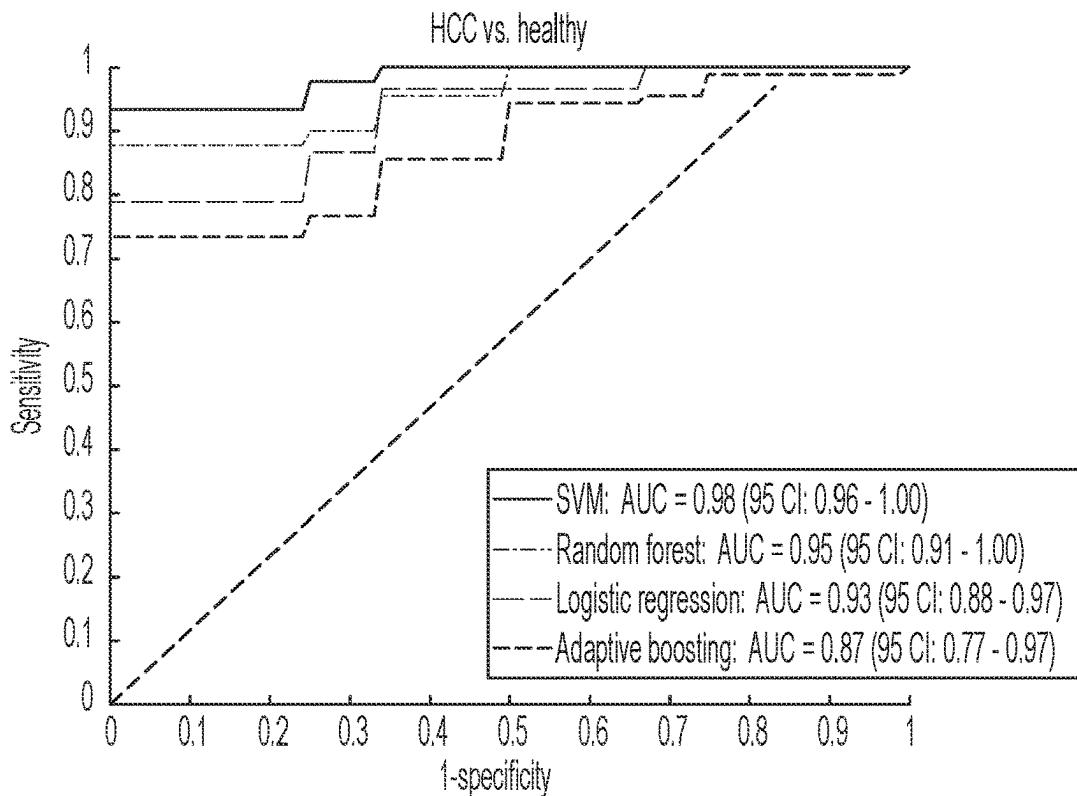


FIG. S10b

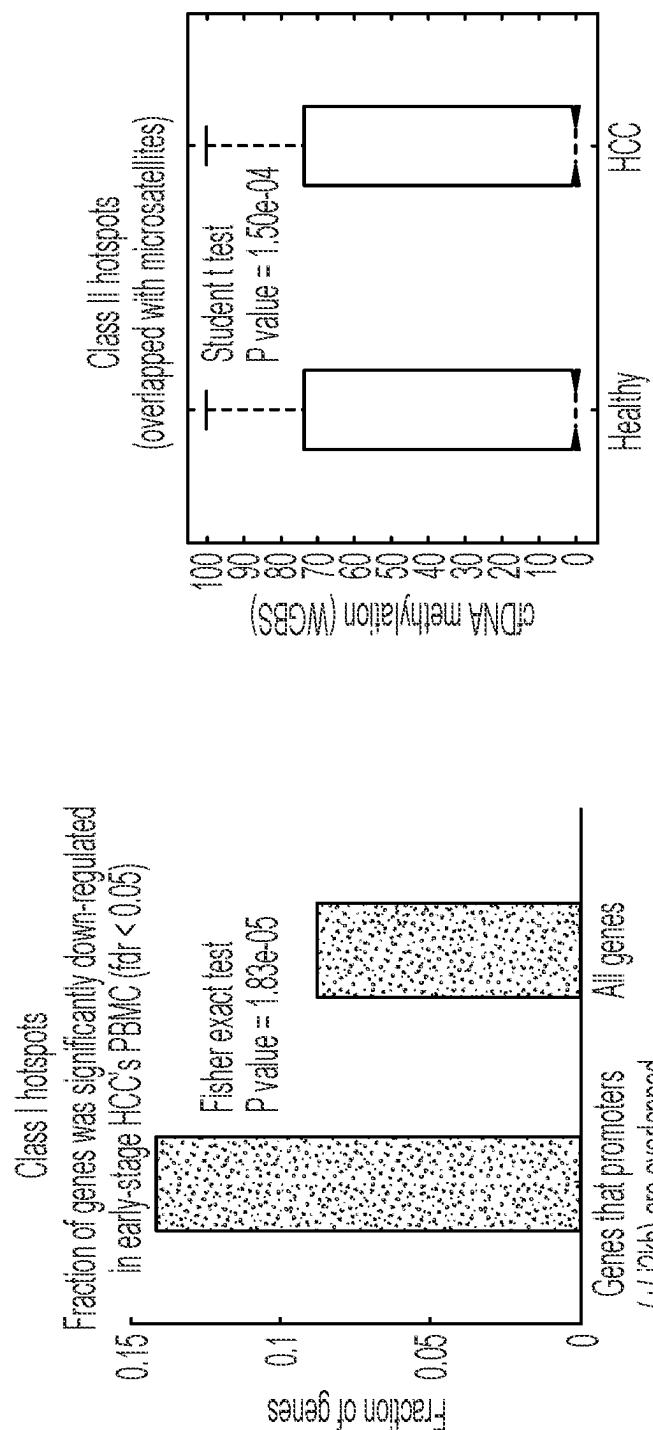


FIG. S11b

FIG. S11a

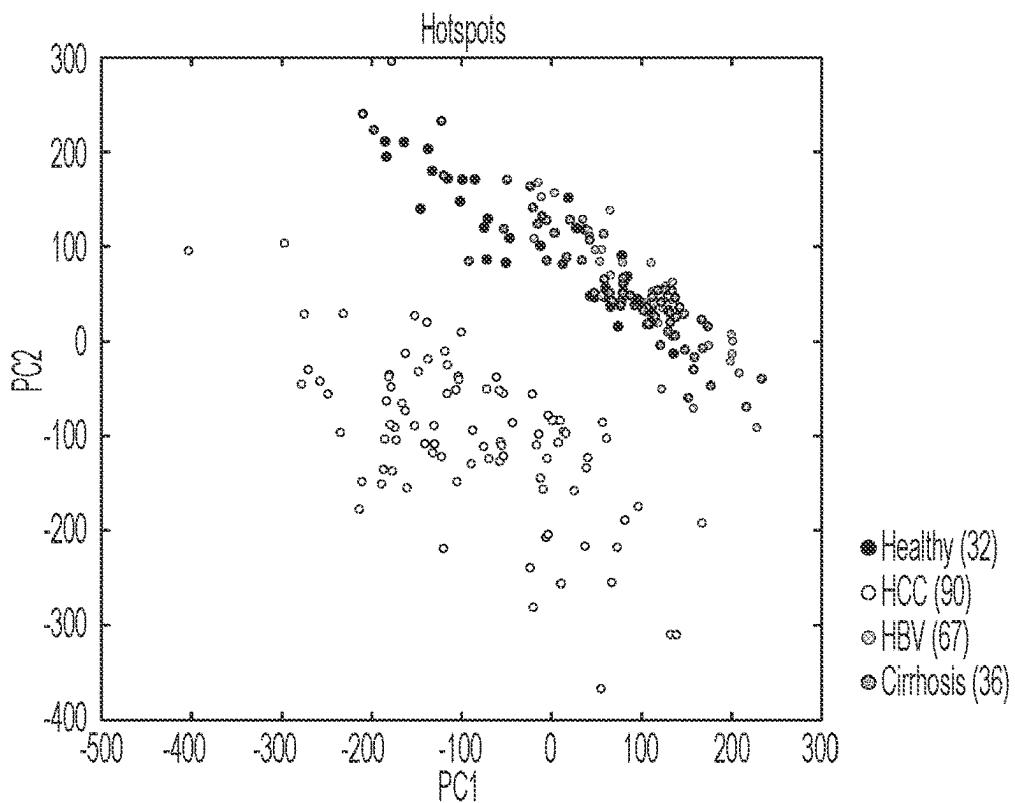


FIG. S12a

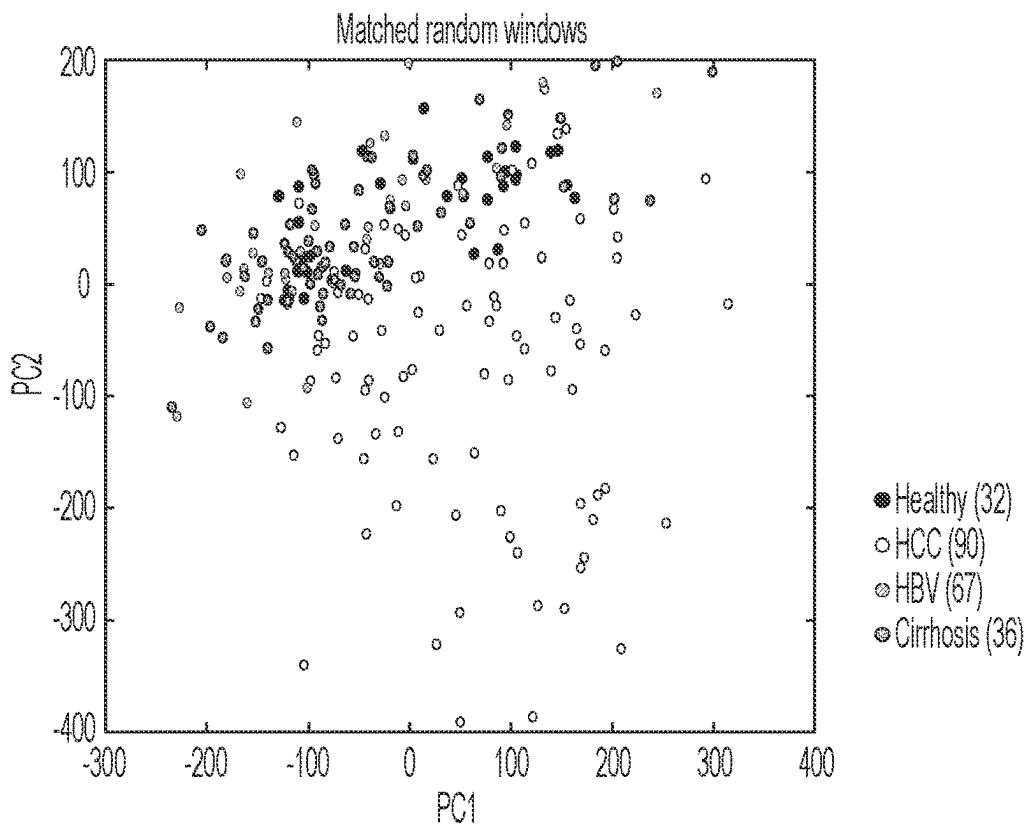


FIG. S12b

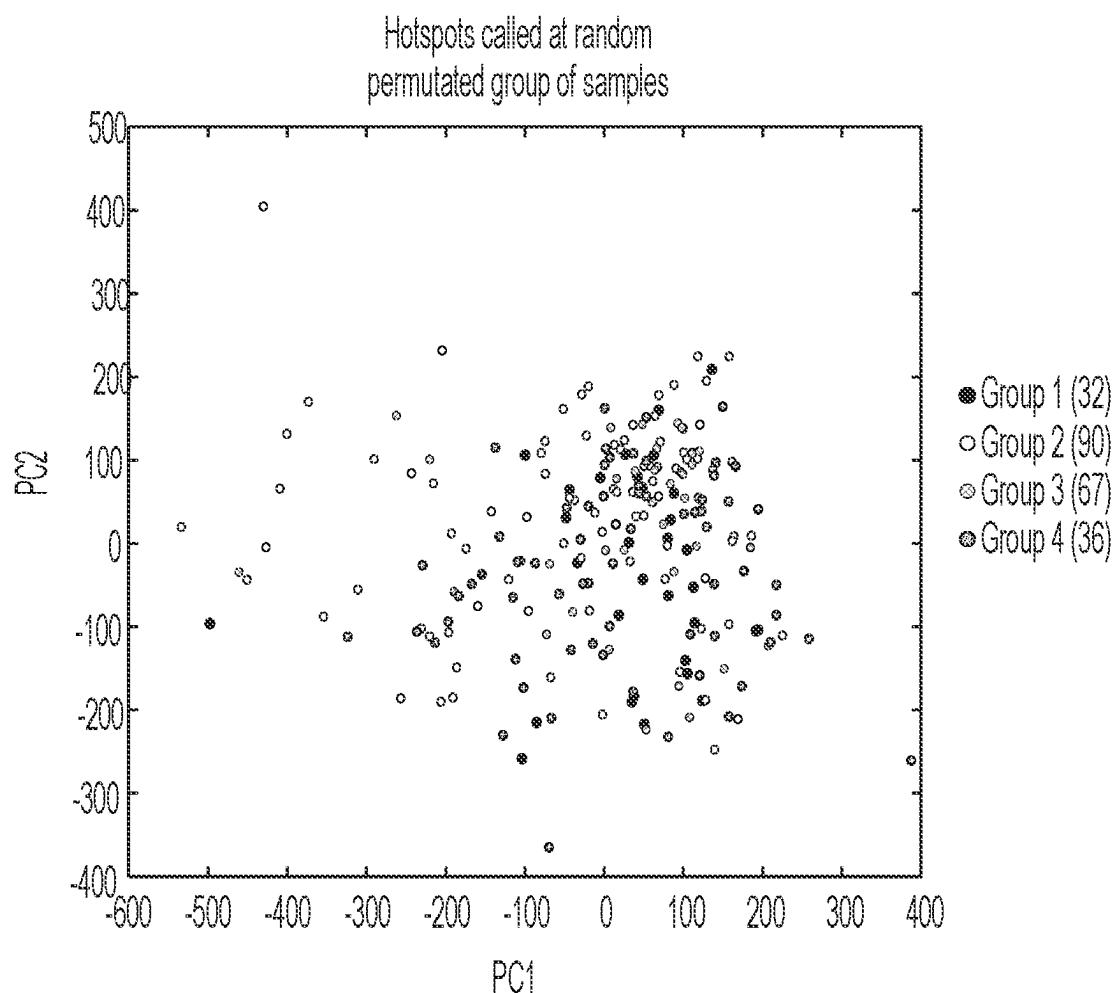


FIG. S12c

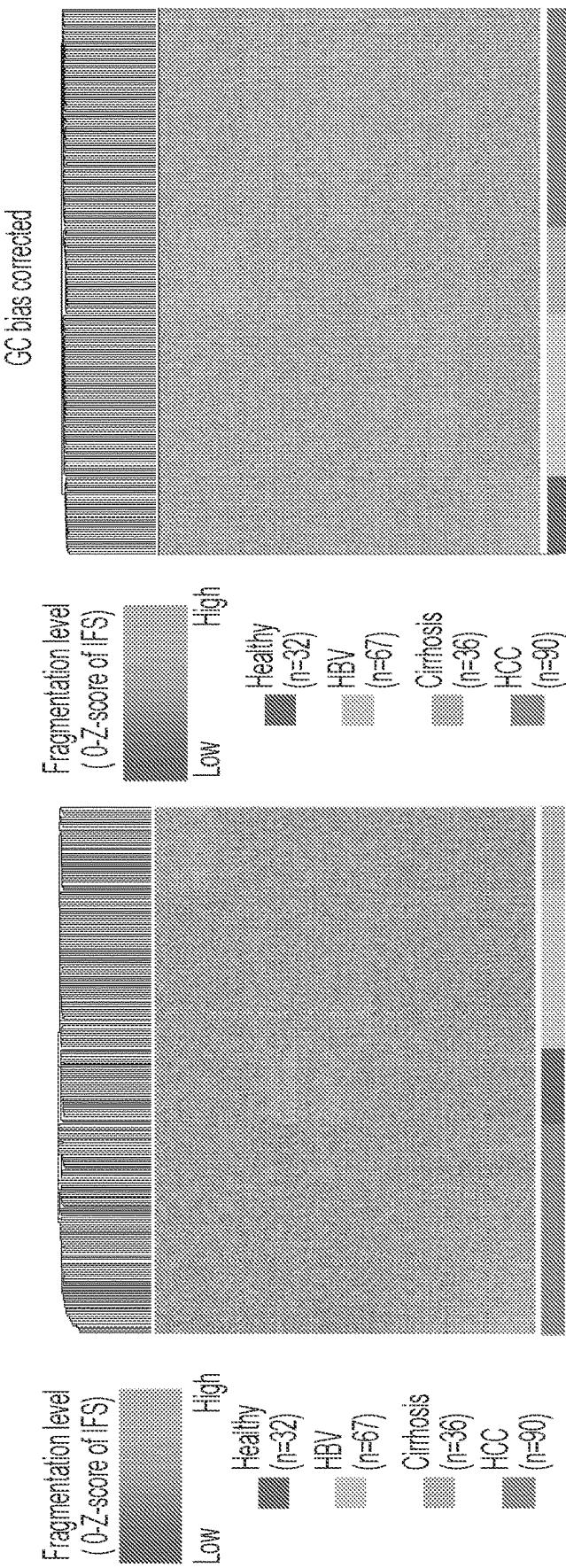


FIG. S13

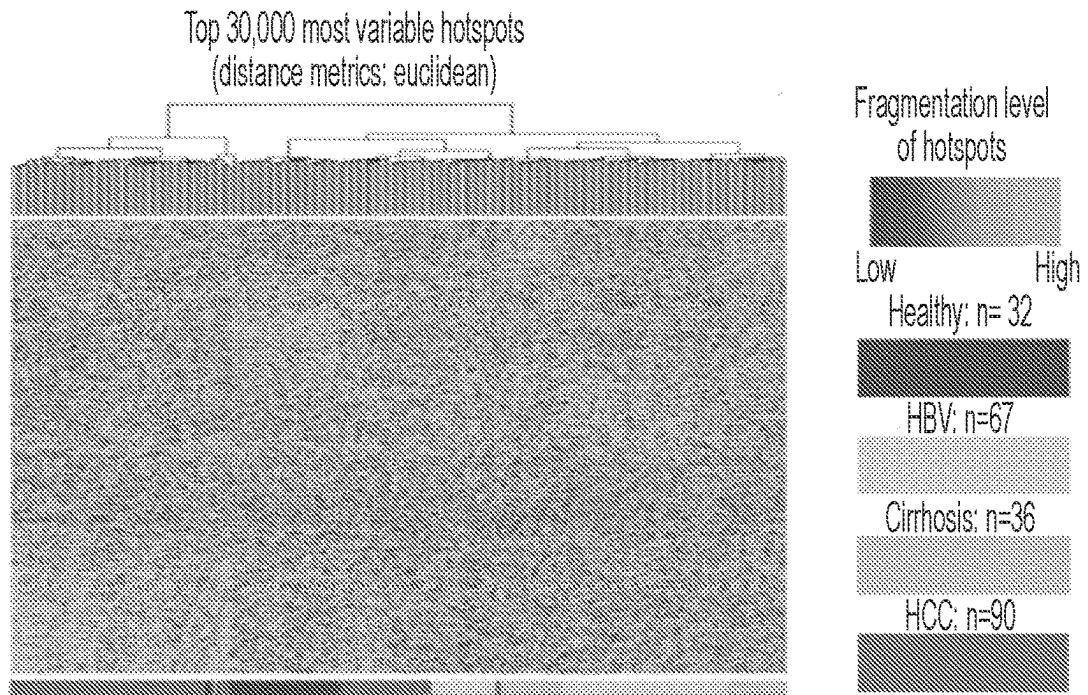


FIG. S14a

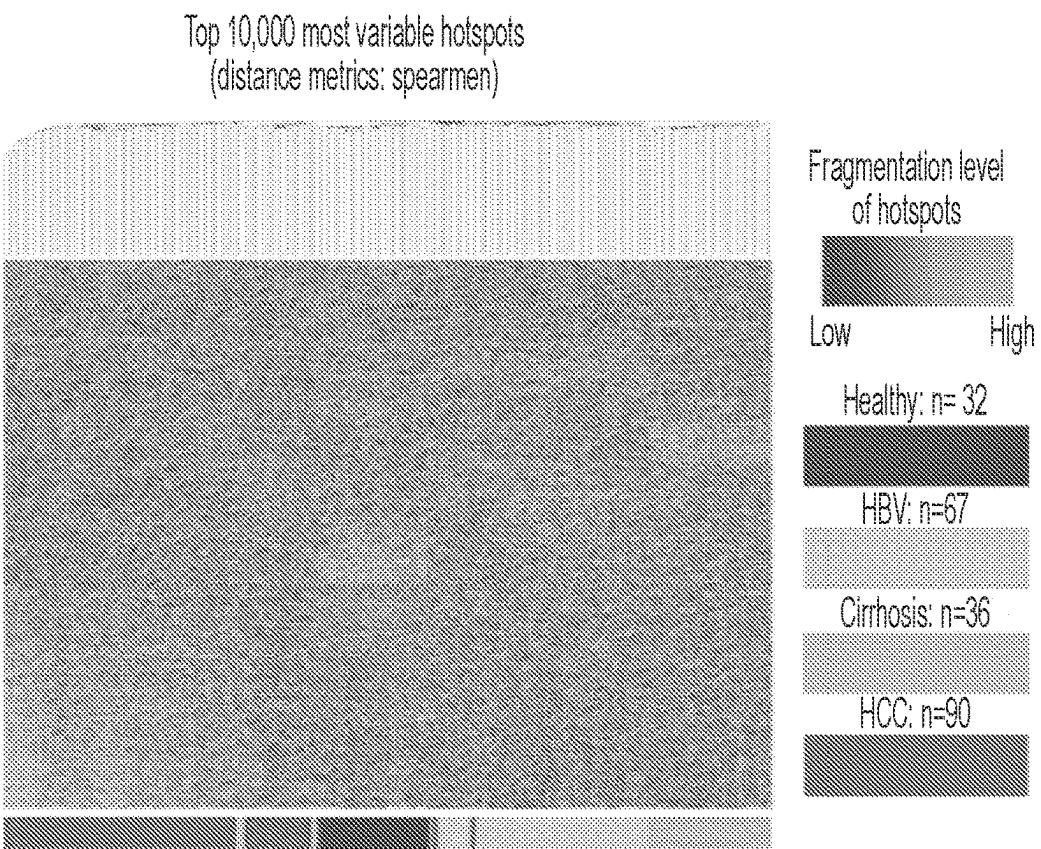


FIG. S14b

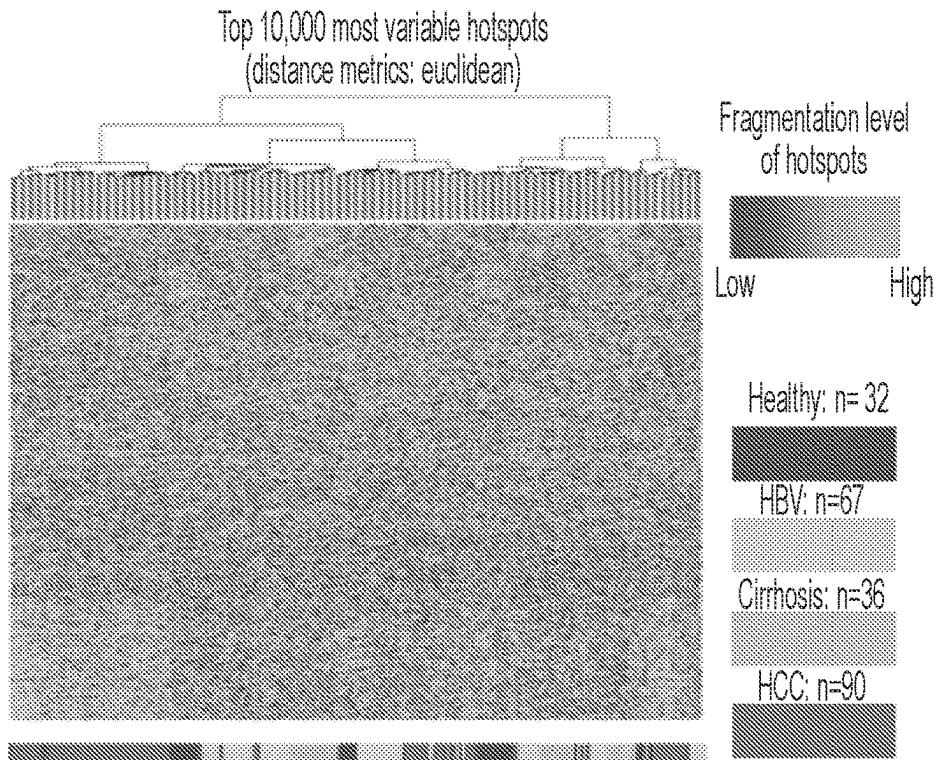


FIG. S14c

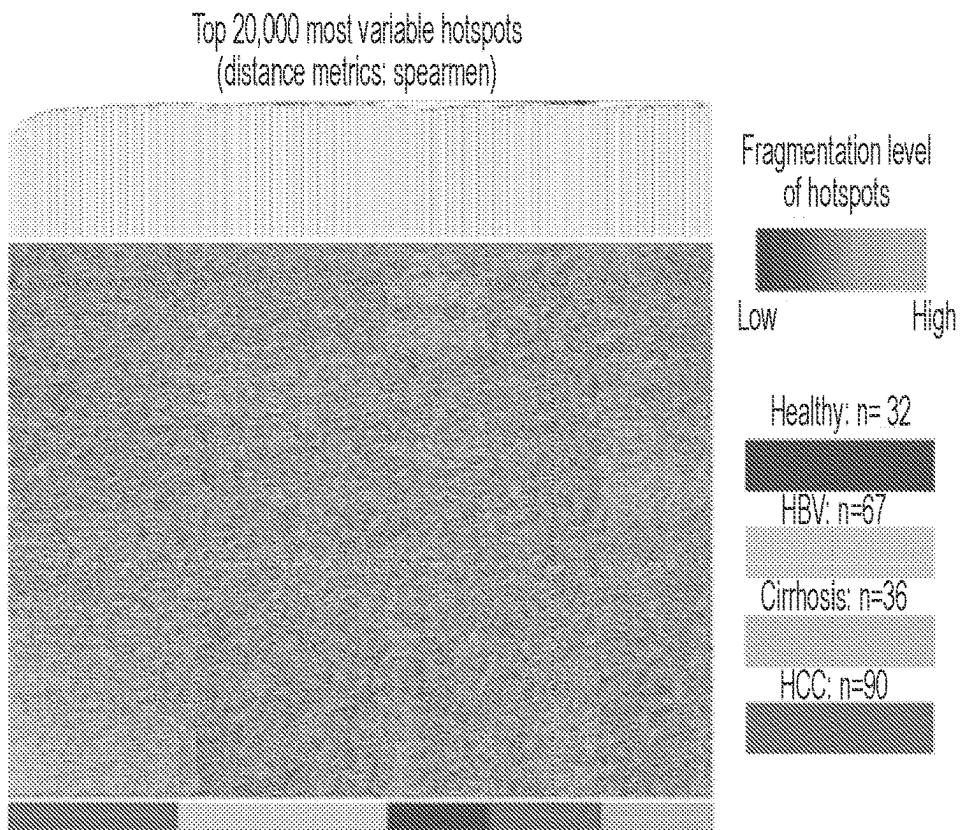


FIG. S14d

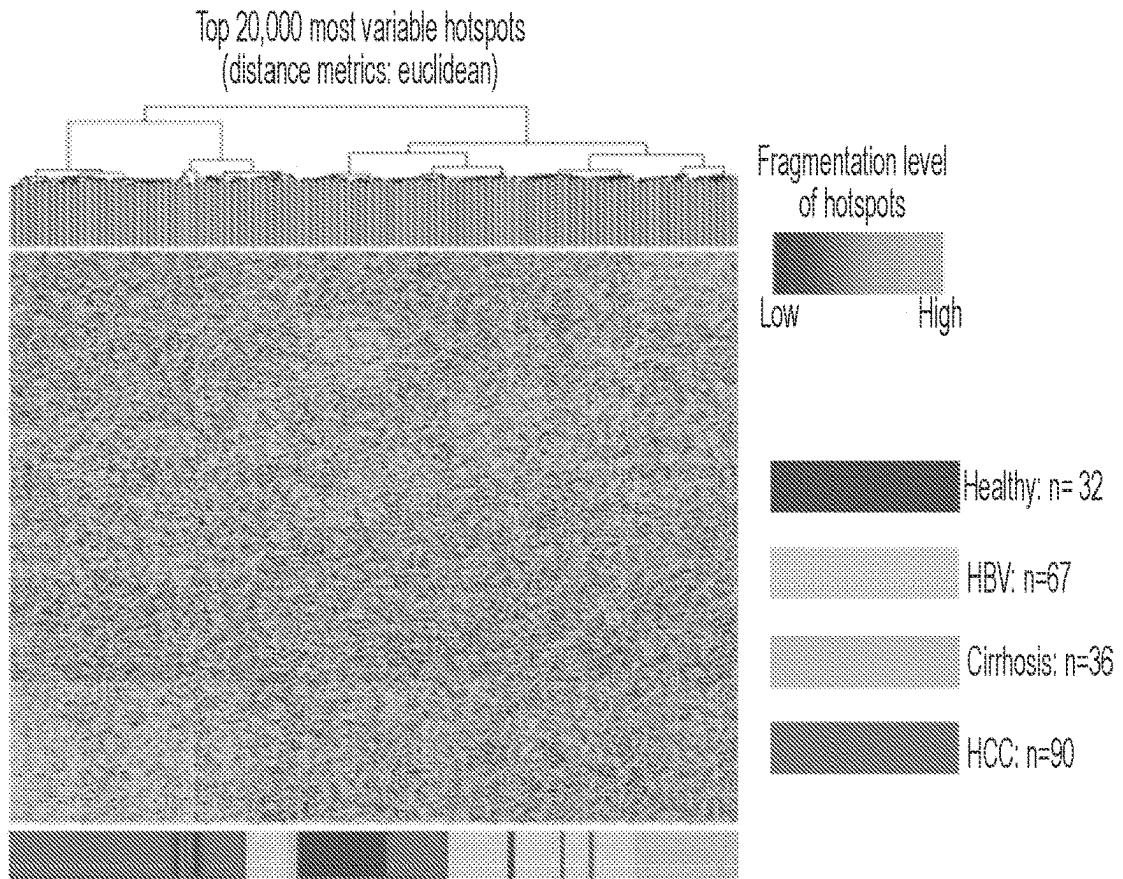


FIG. S14e

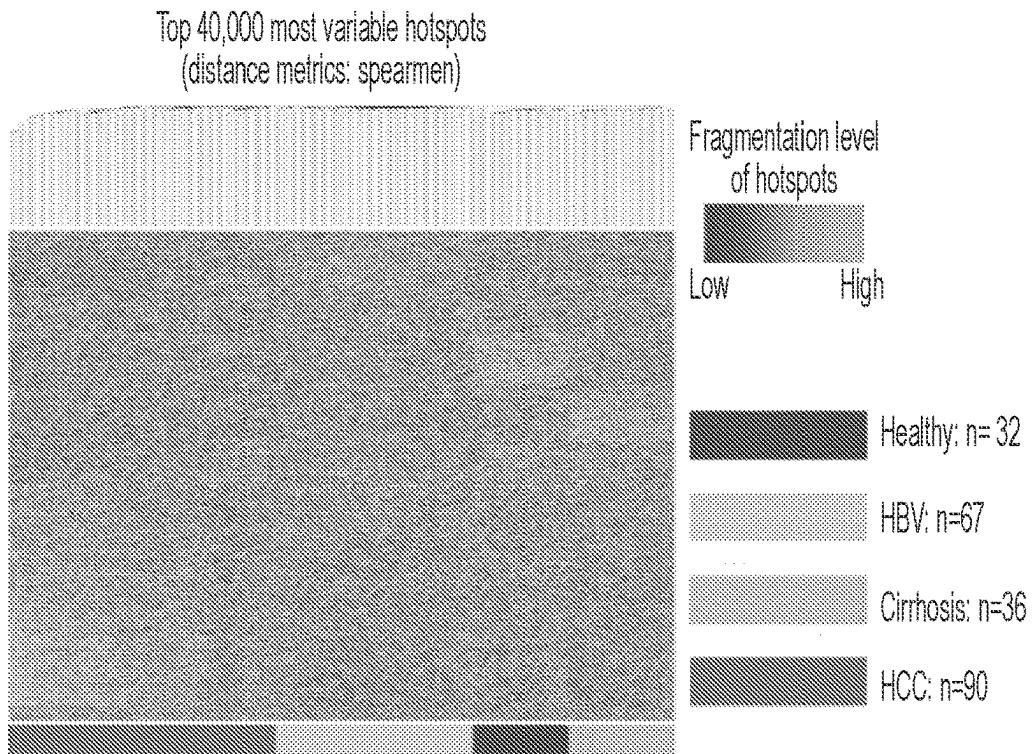


FIG. S14f

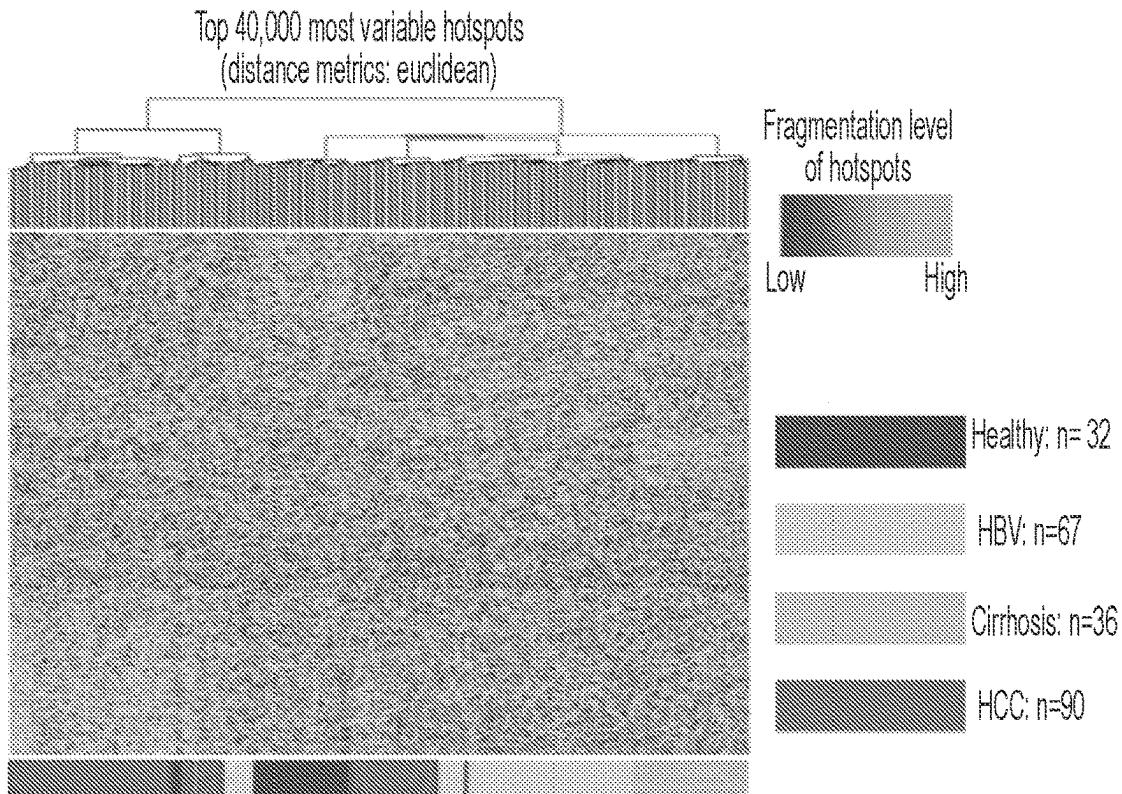


FIG. S14g

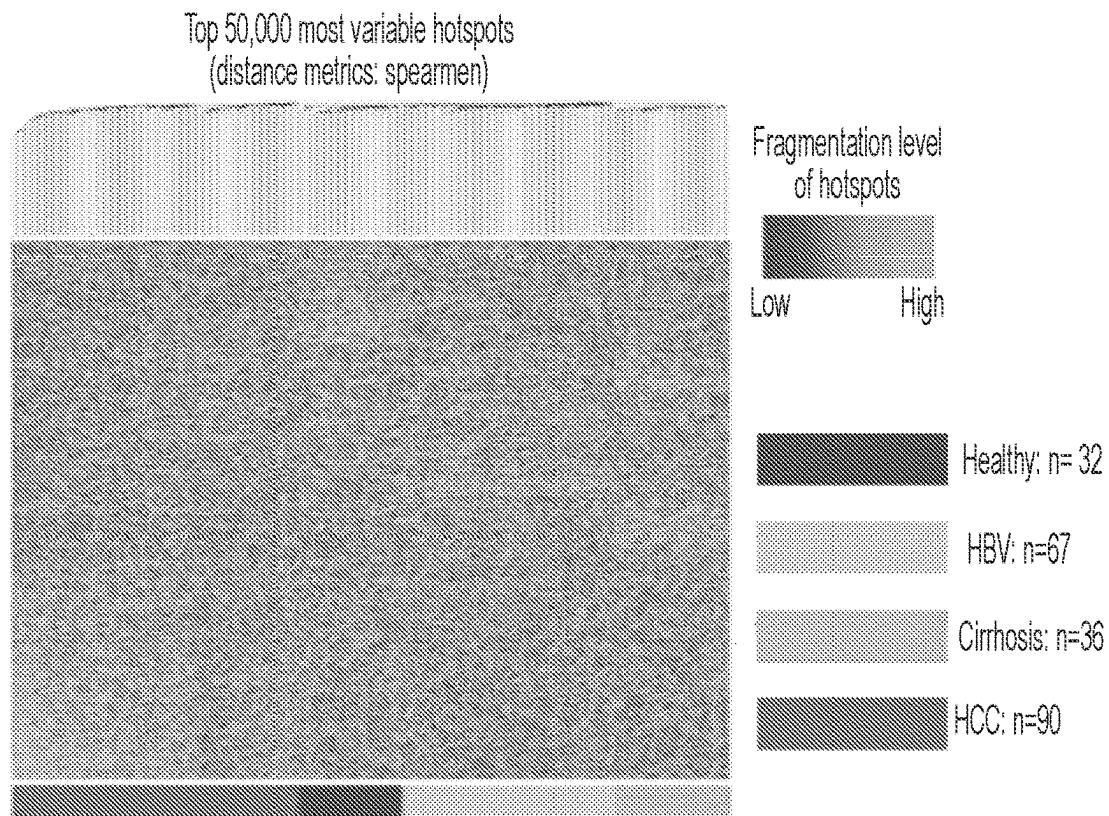


FIG. S14h

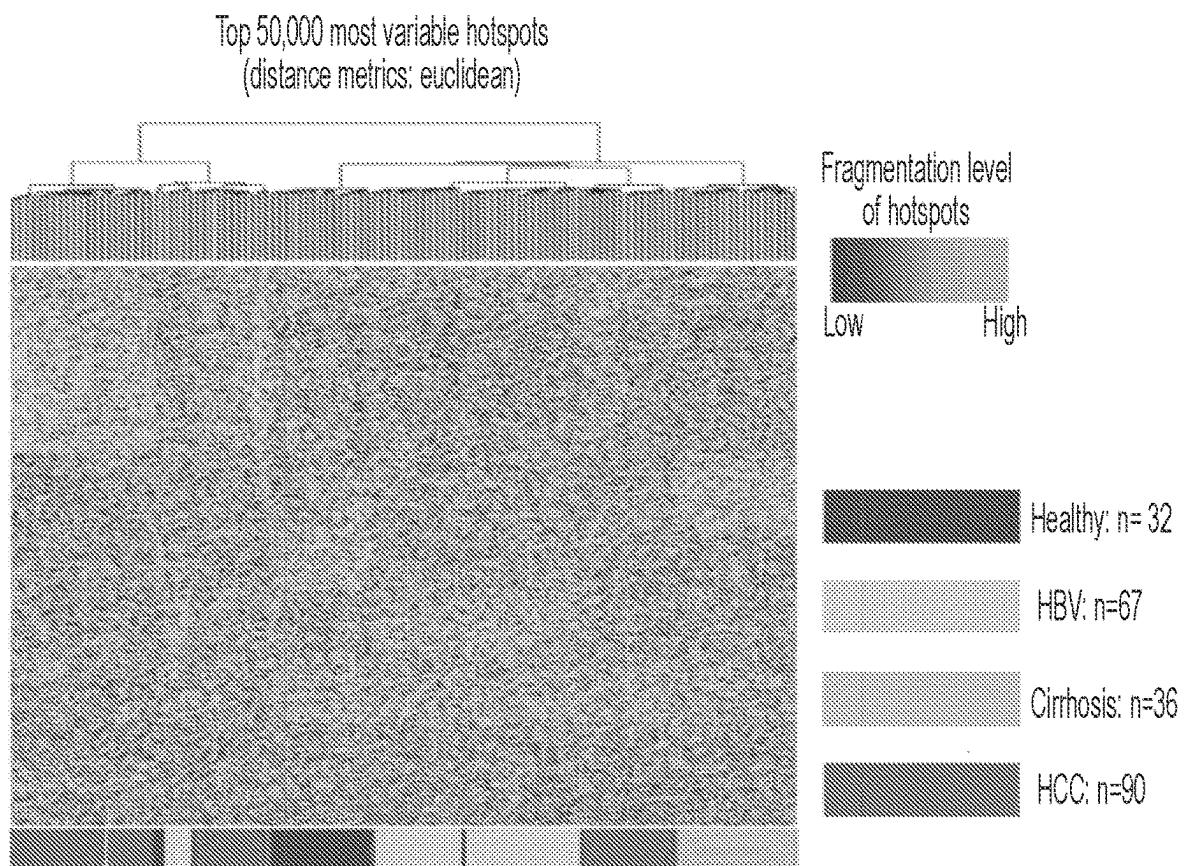


FIG. S14i

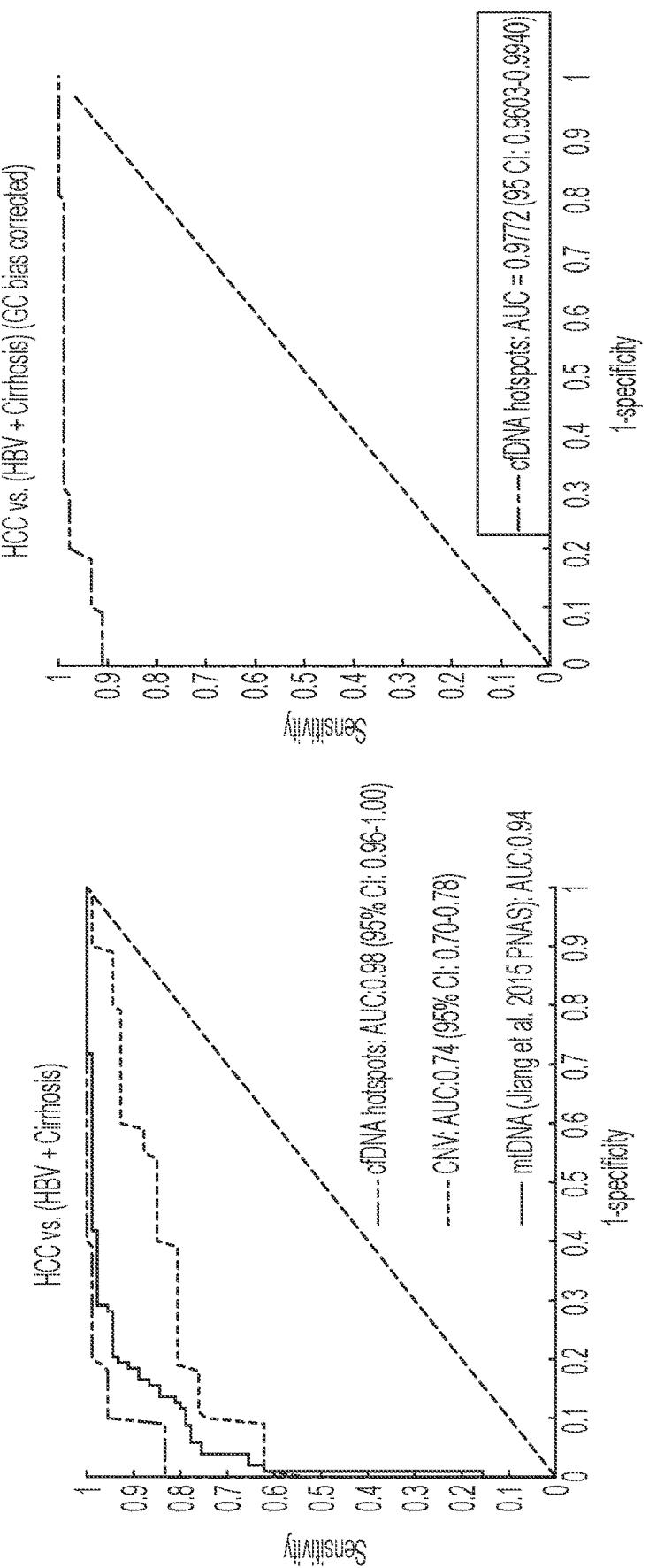


FIG. S15a

FIG. S15b

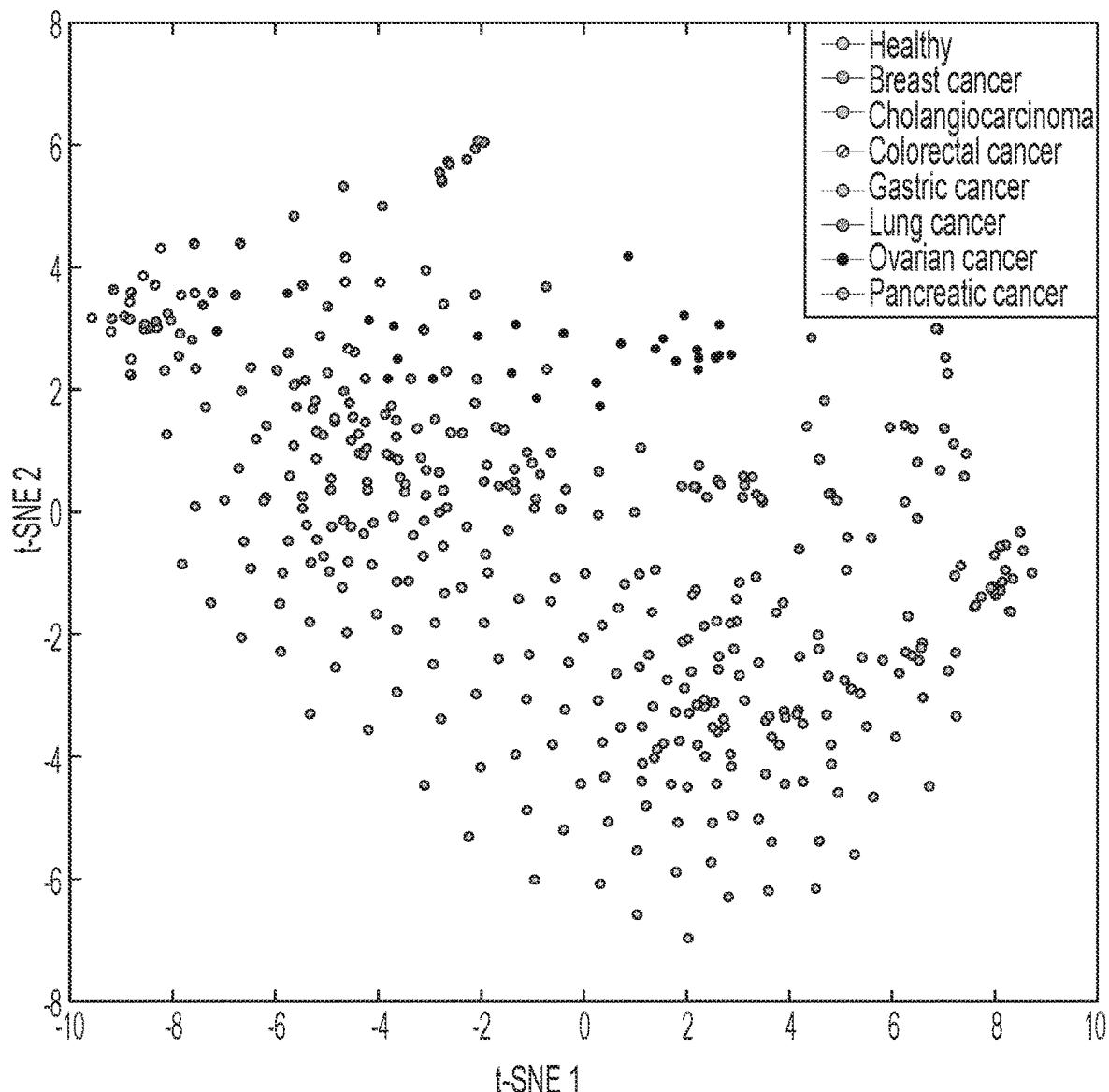
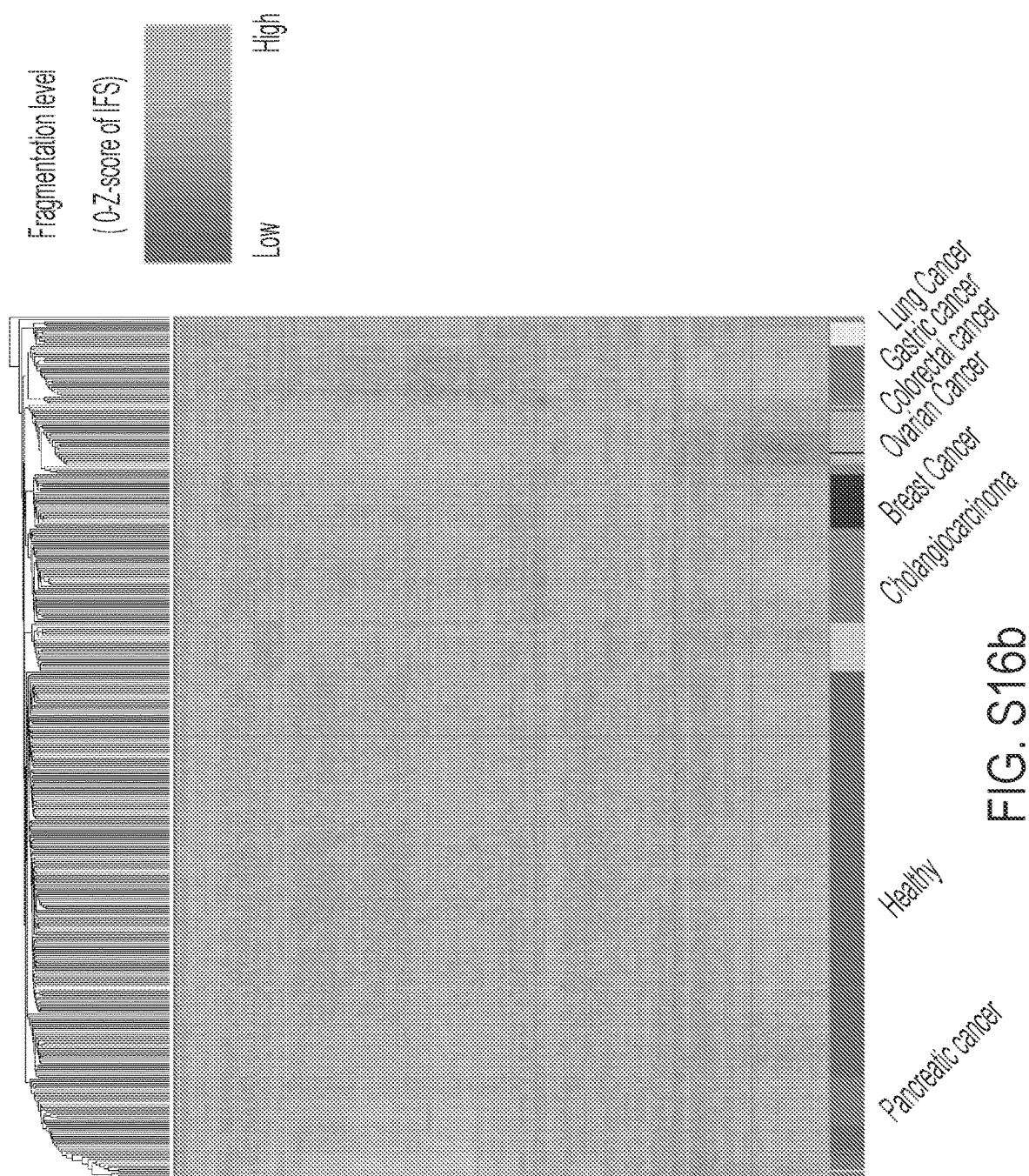


FIG. S16a



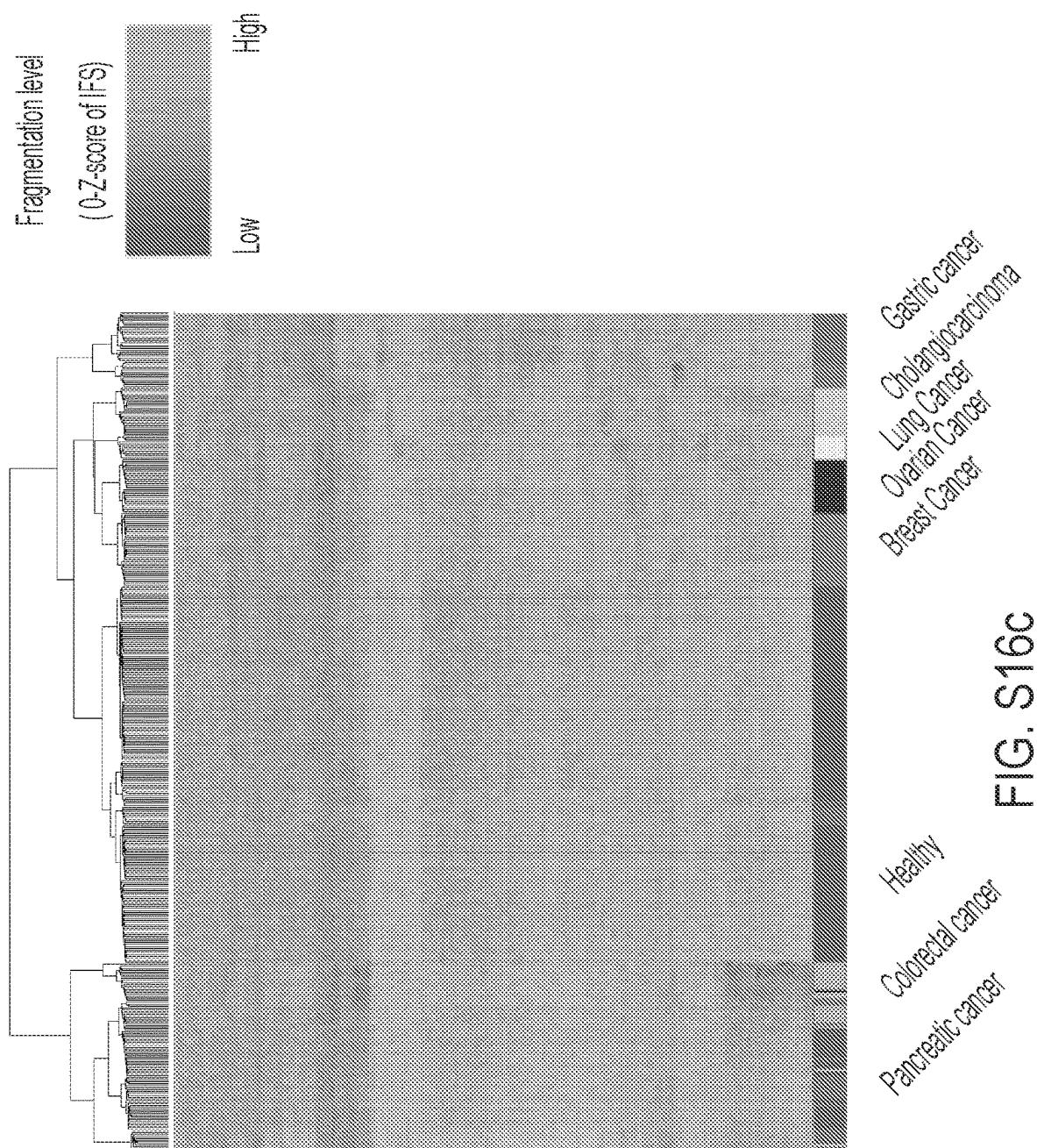


FIG. S16c

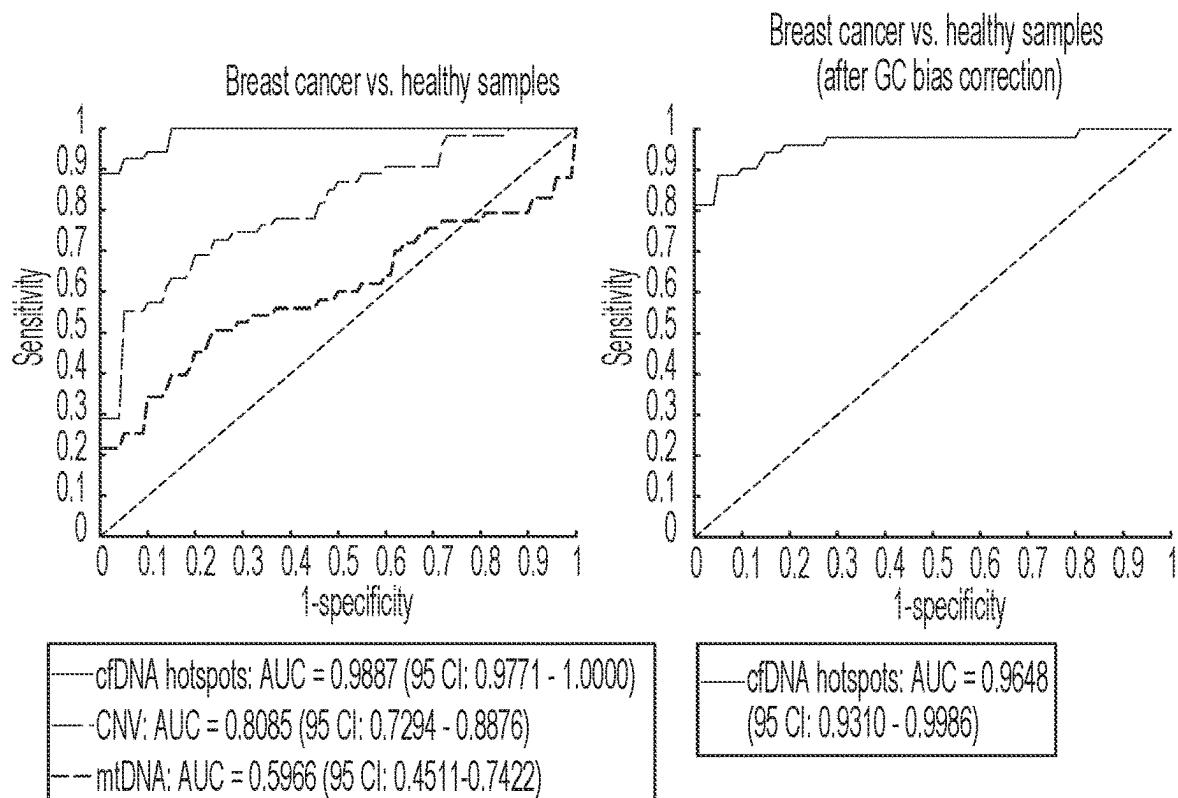


FIG. S17a

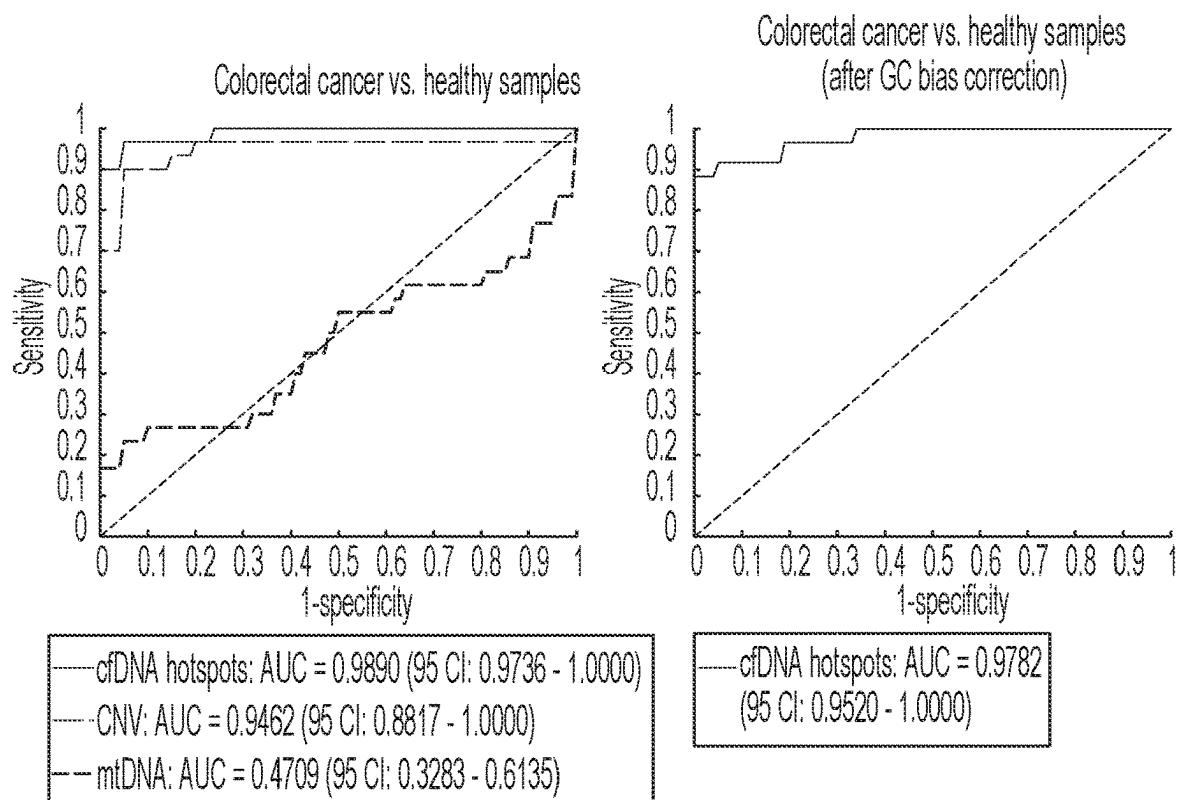


FIG. S17b

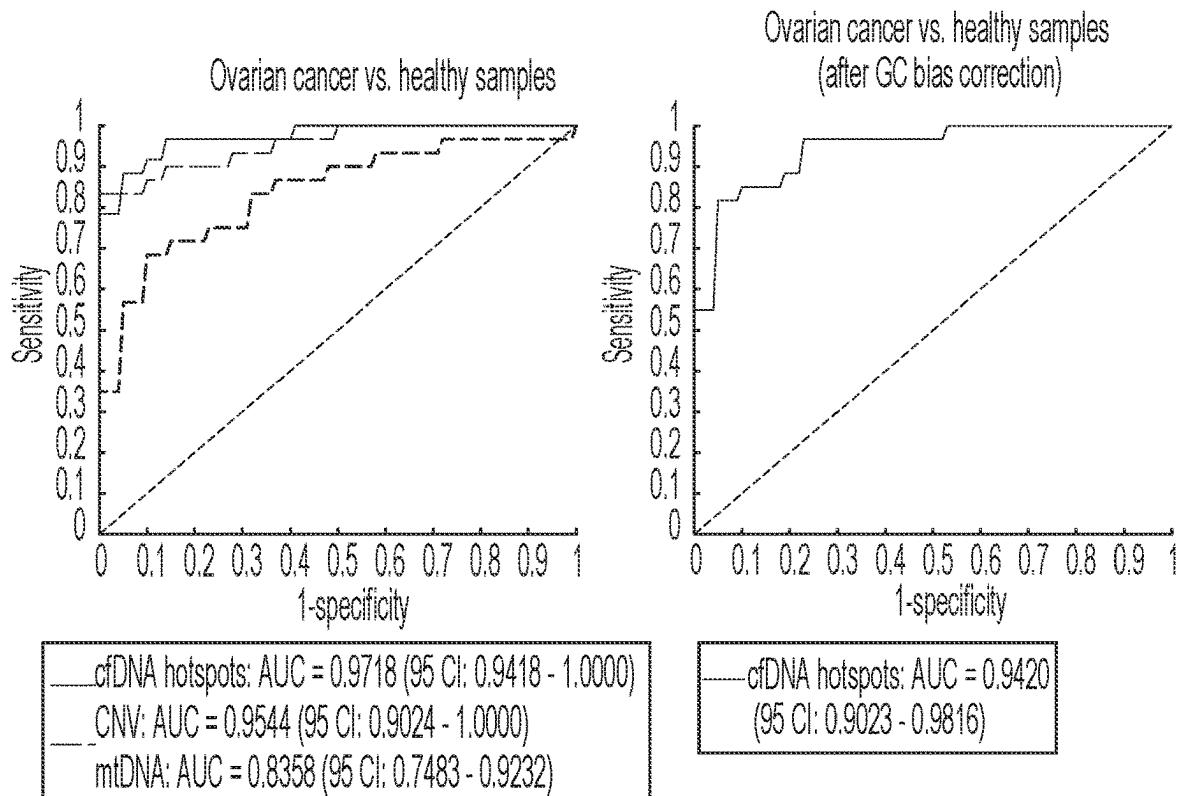


FIG. S17c

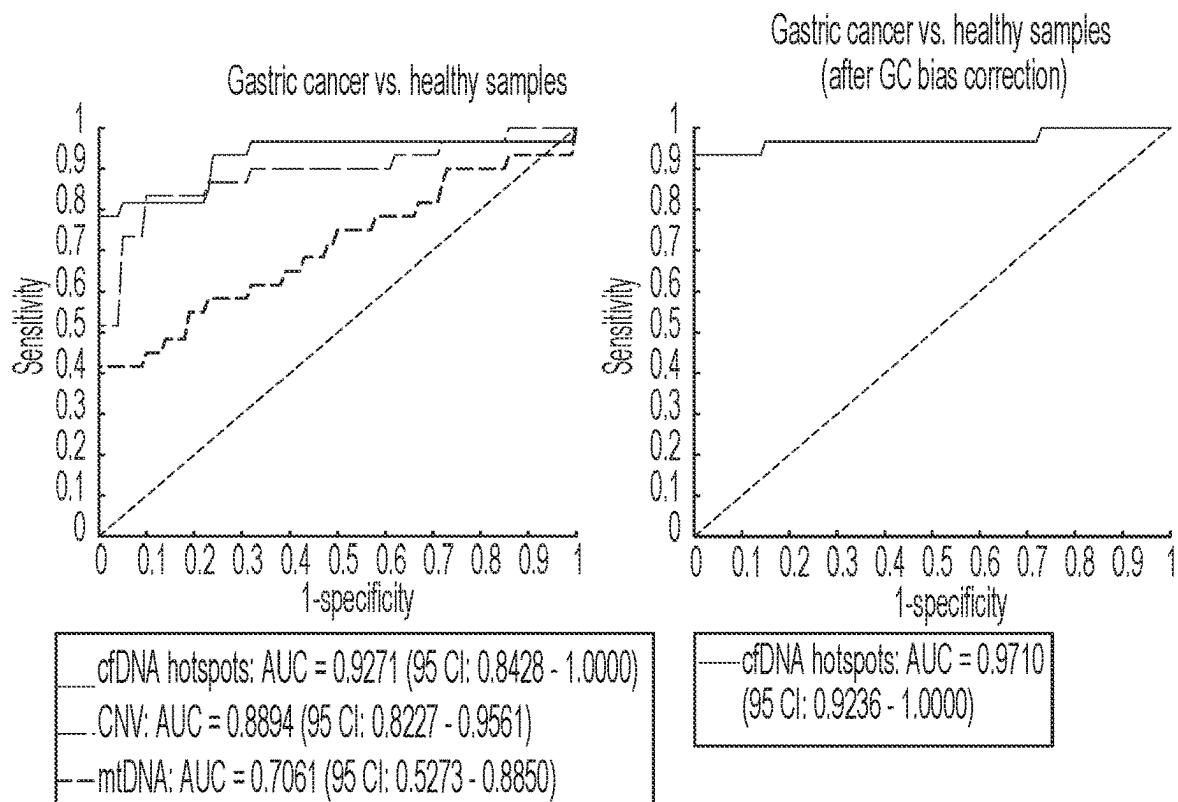


FIG. S17d

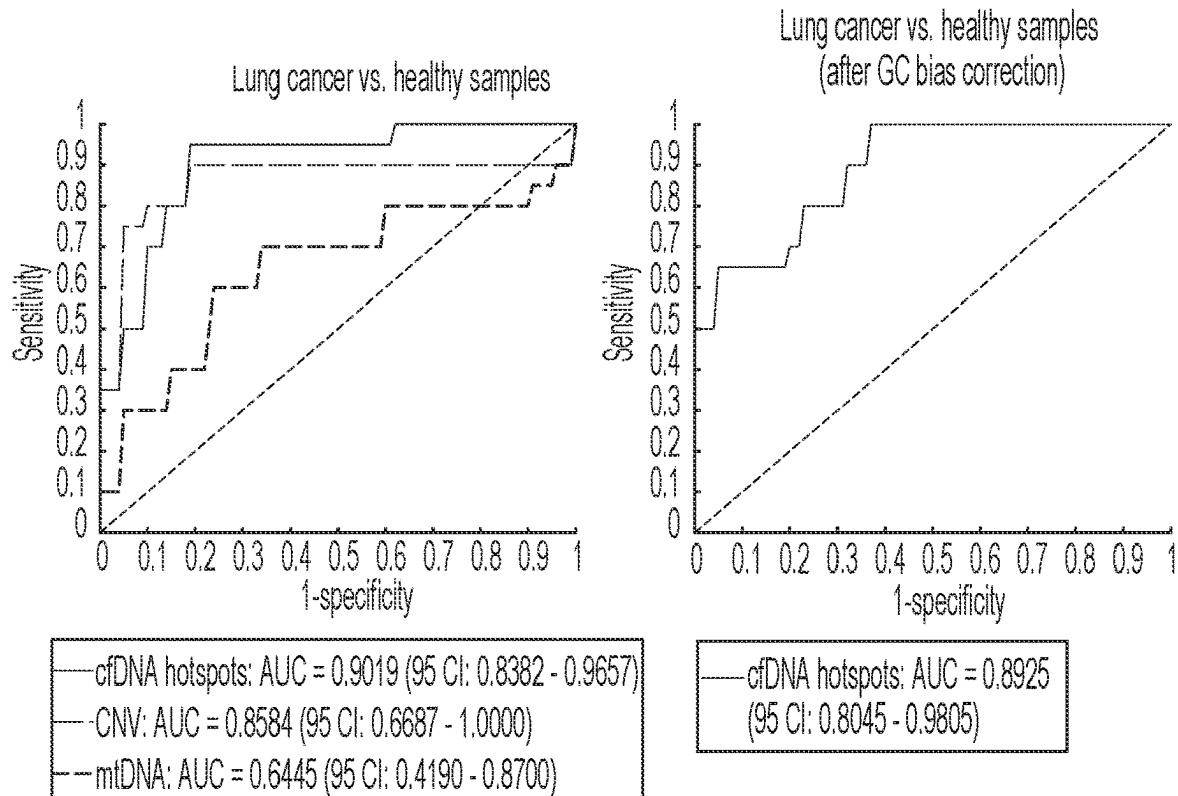


FIG. S17e

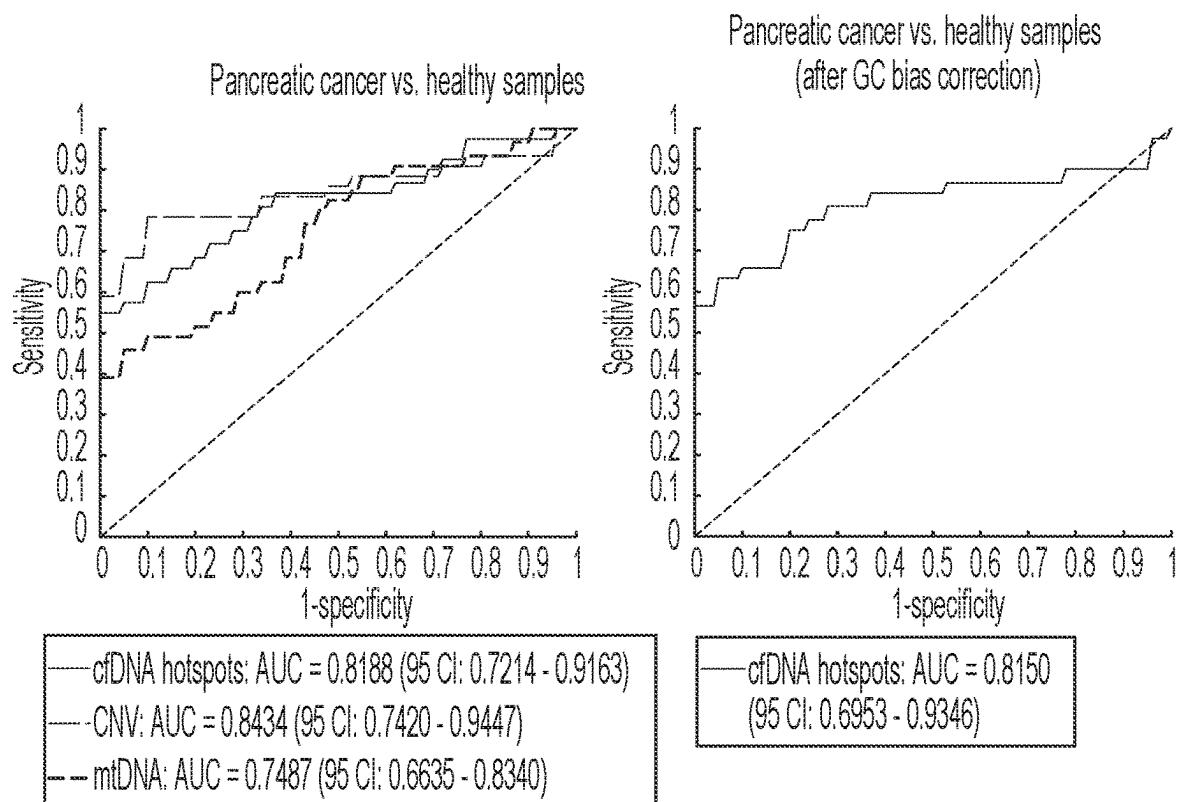


FIG. S17f

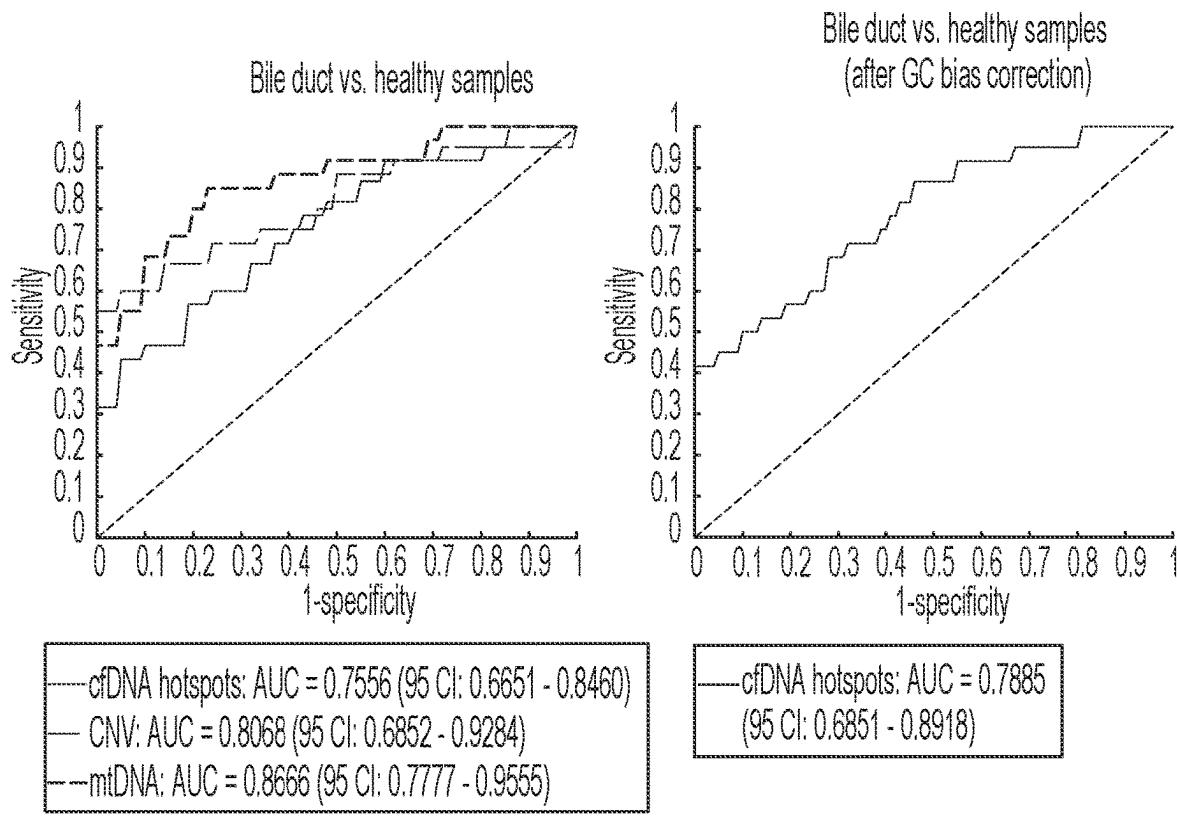


FIG. S17g

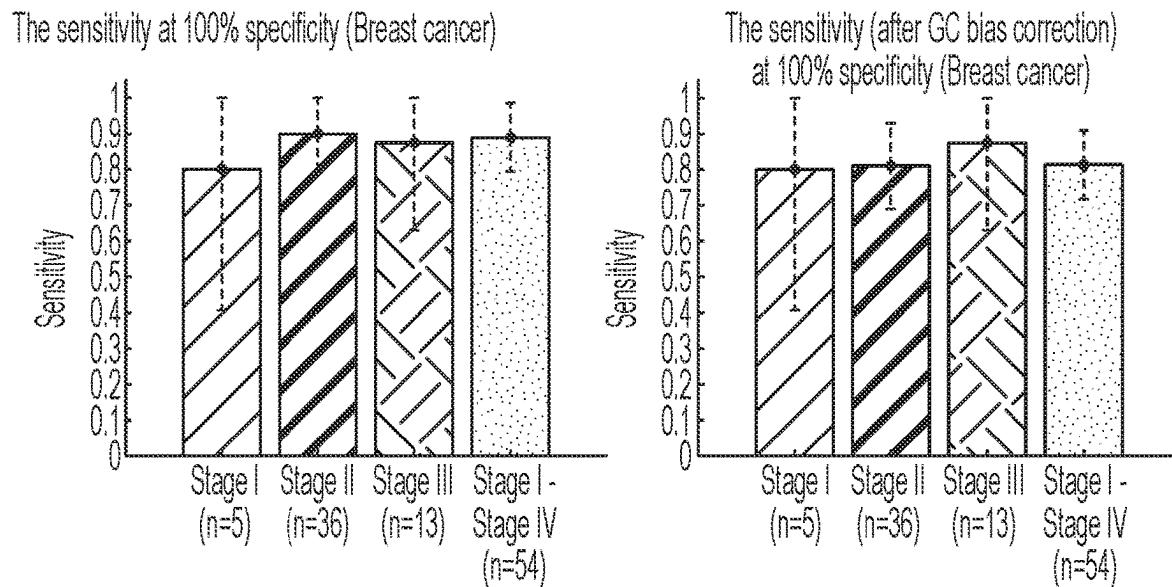


FIG. S18a

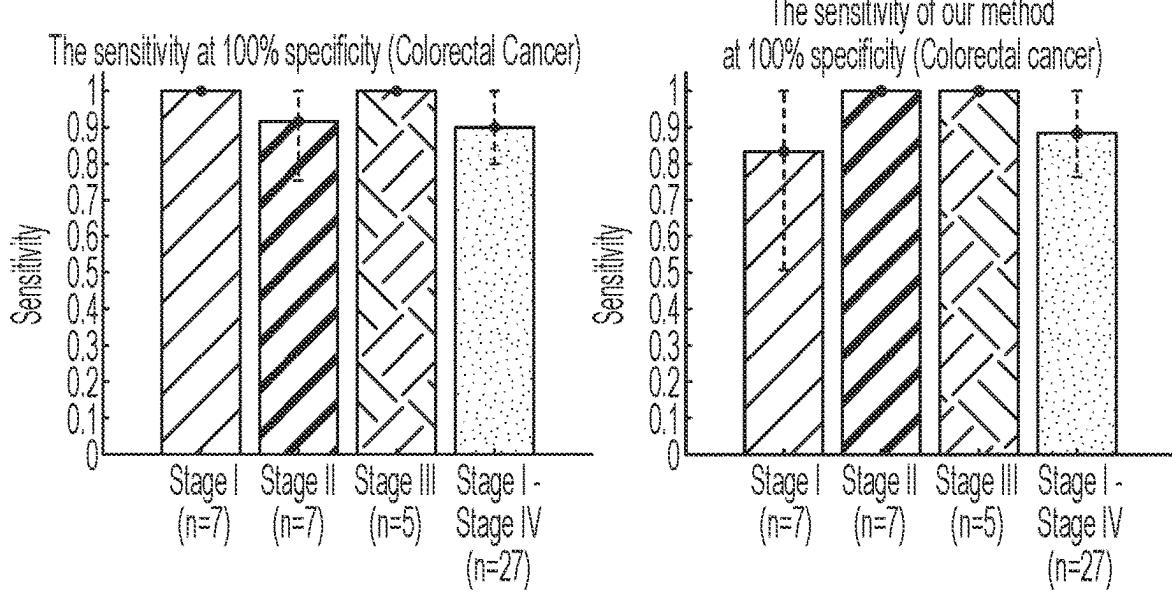


FIG. S18b

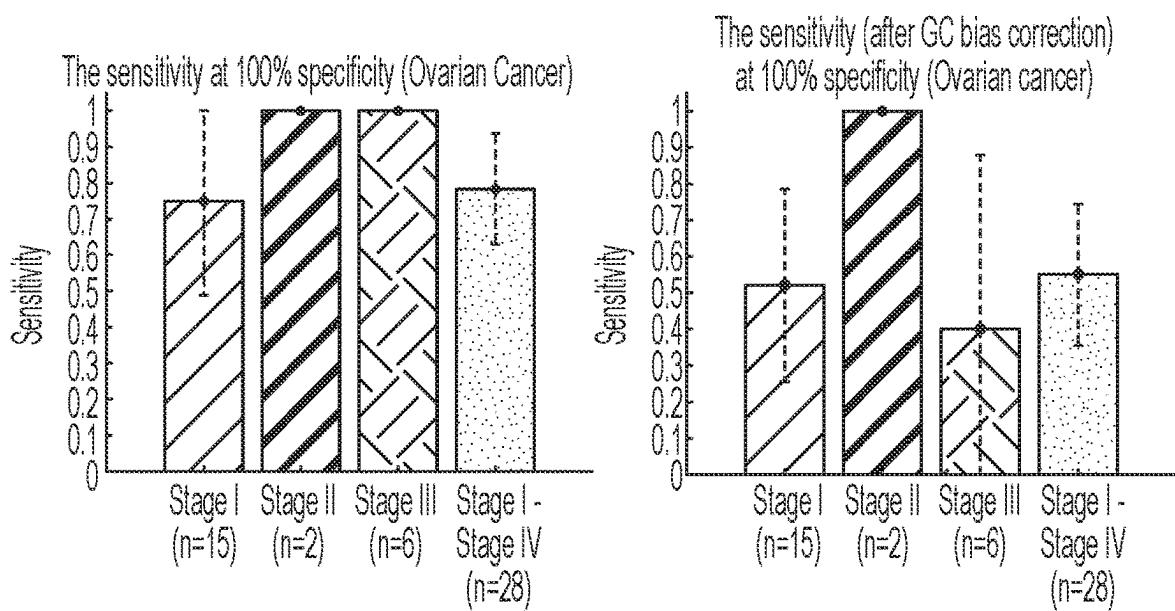


FIG. S18c

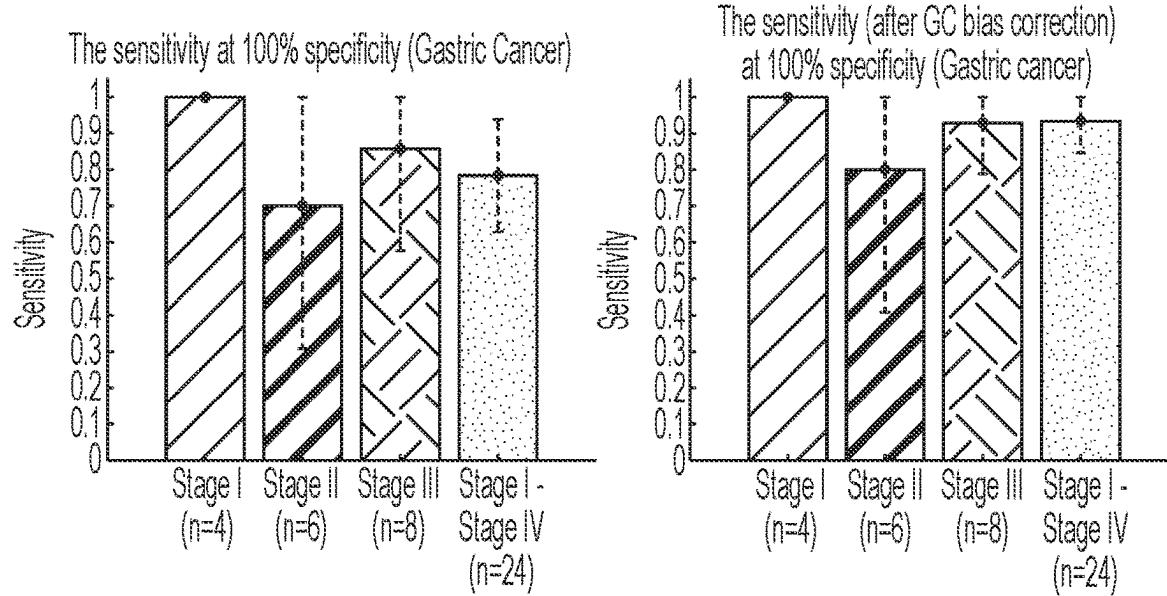


FIG. S18d

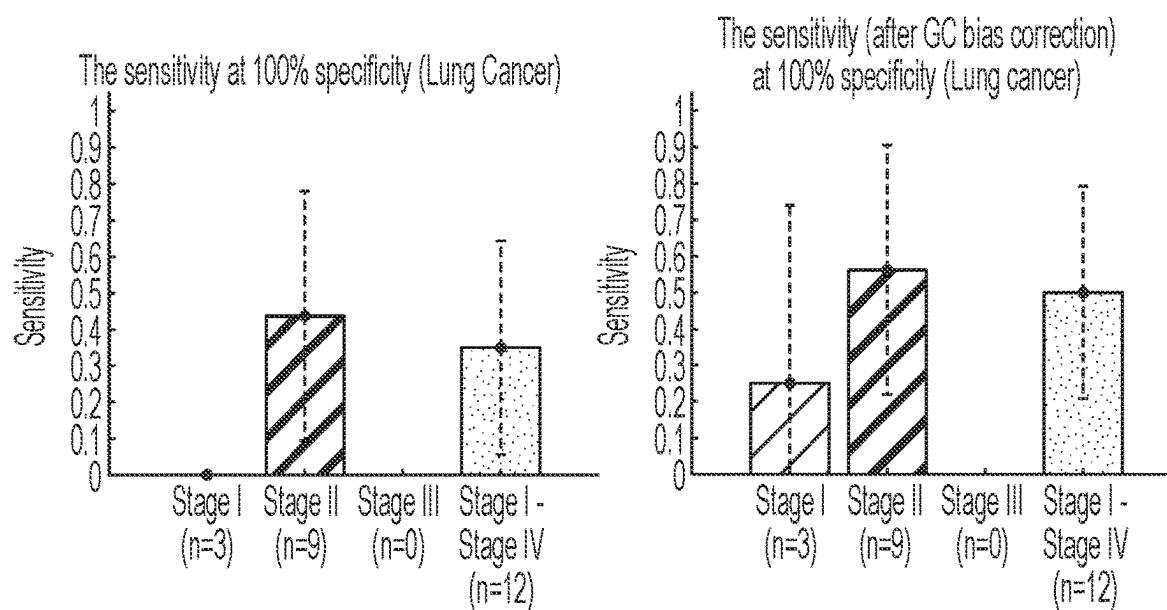


FIG. S18e

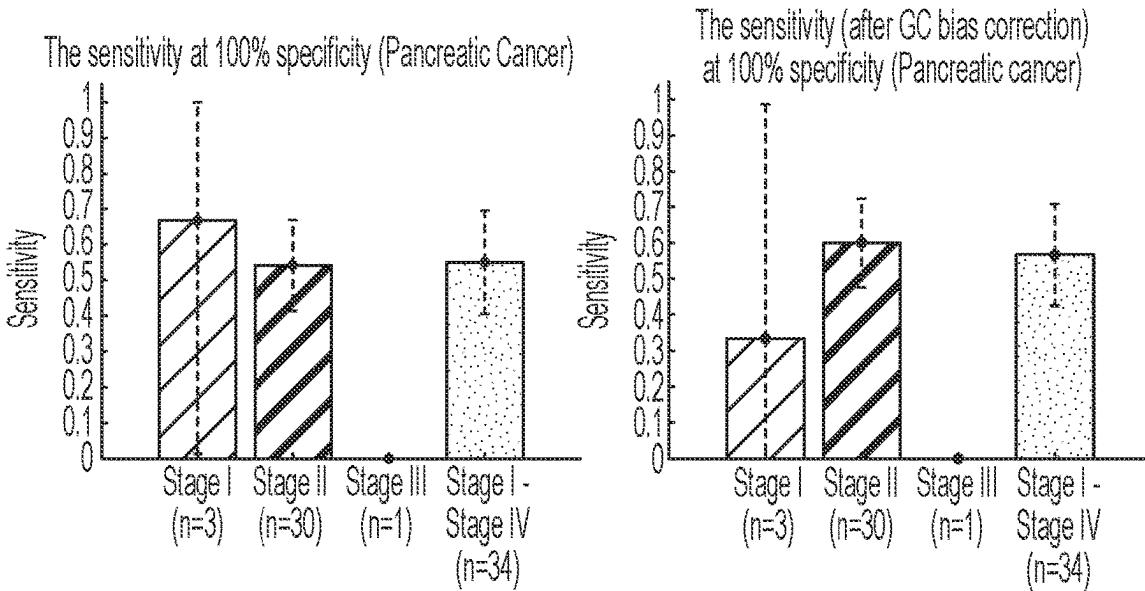


FIG. S18f

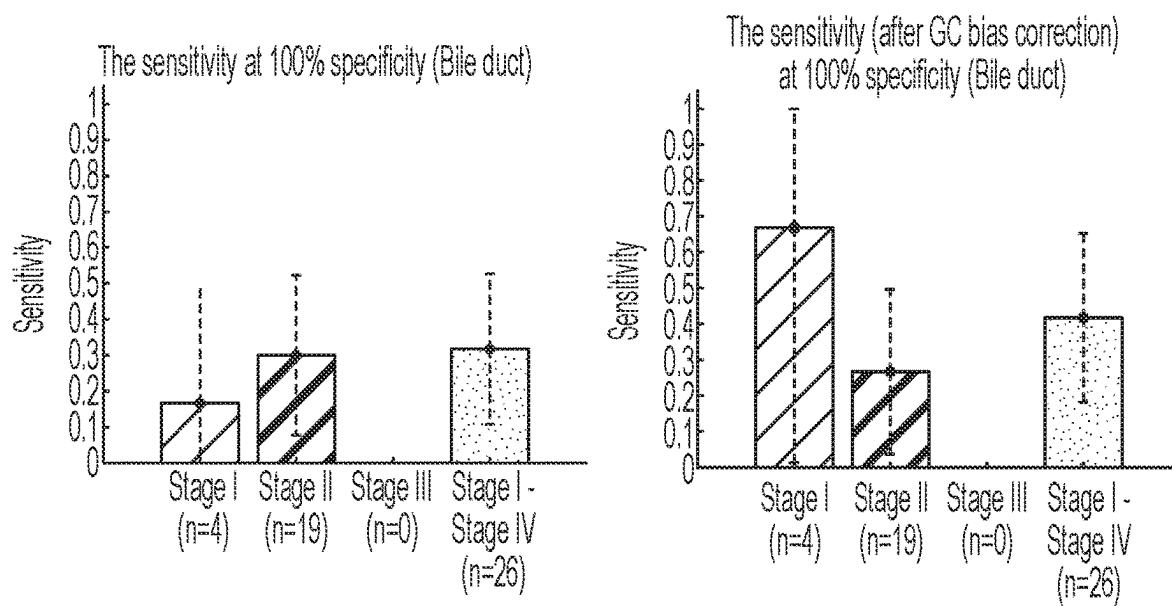


FIG. S18g

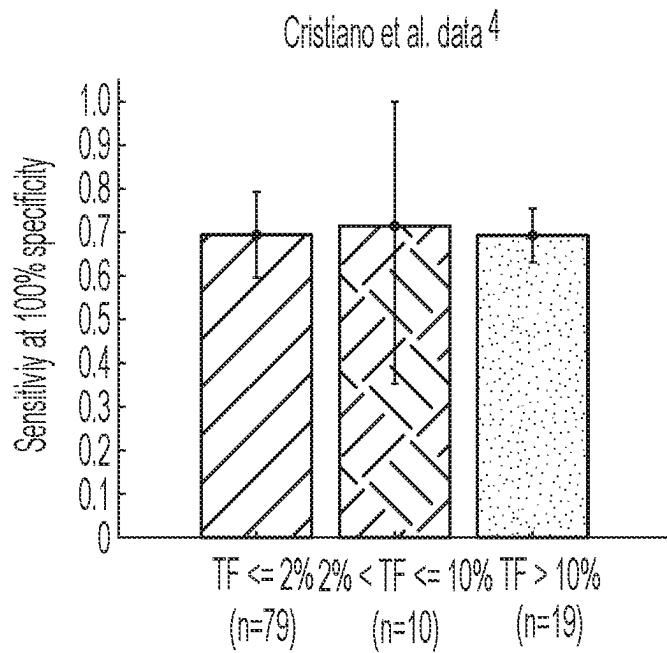


FIG. S19a

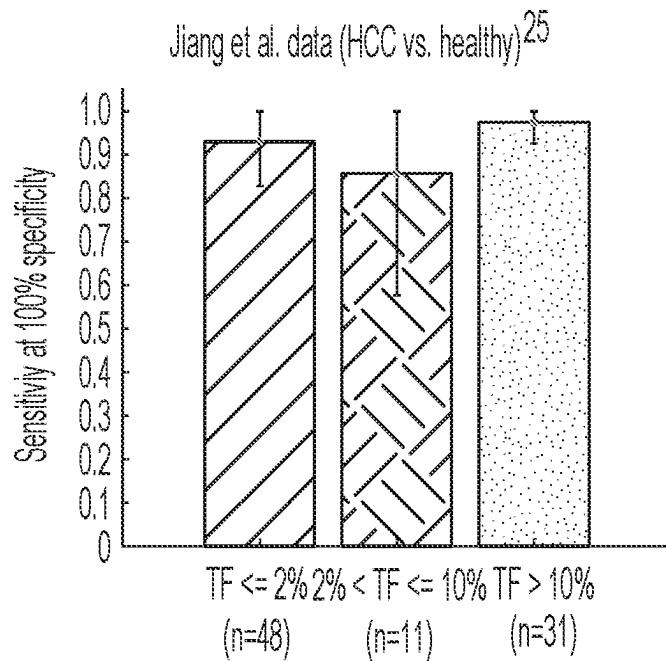


FIG. S19b

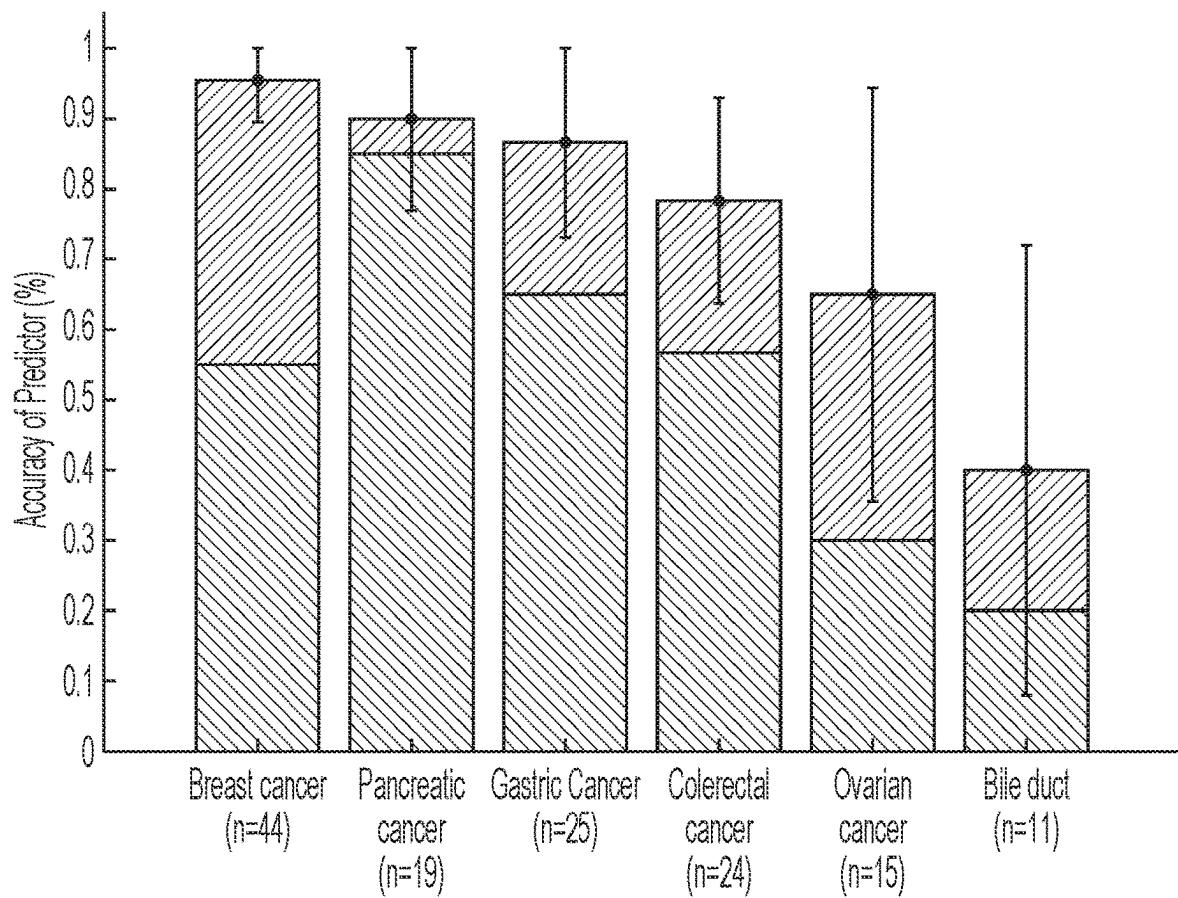


FIG. S20

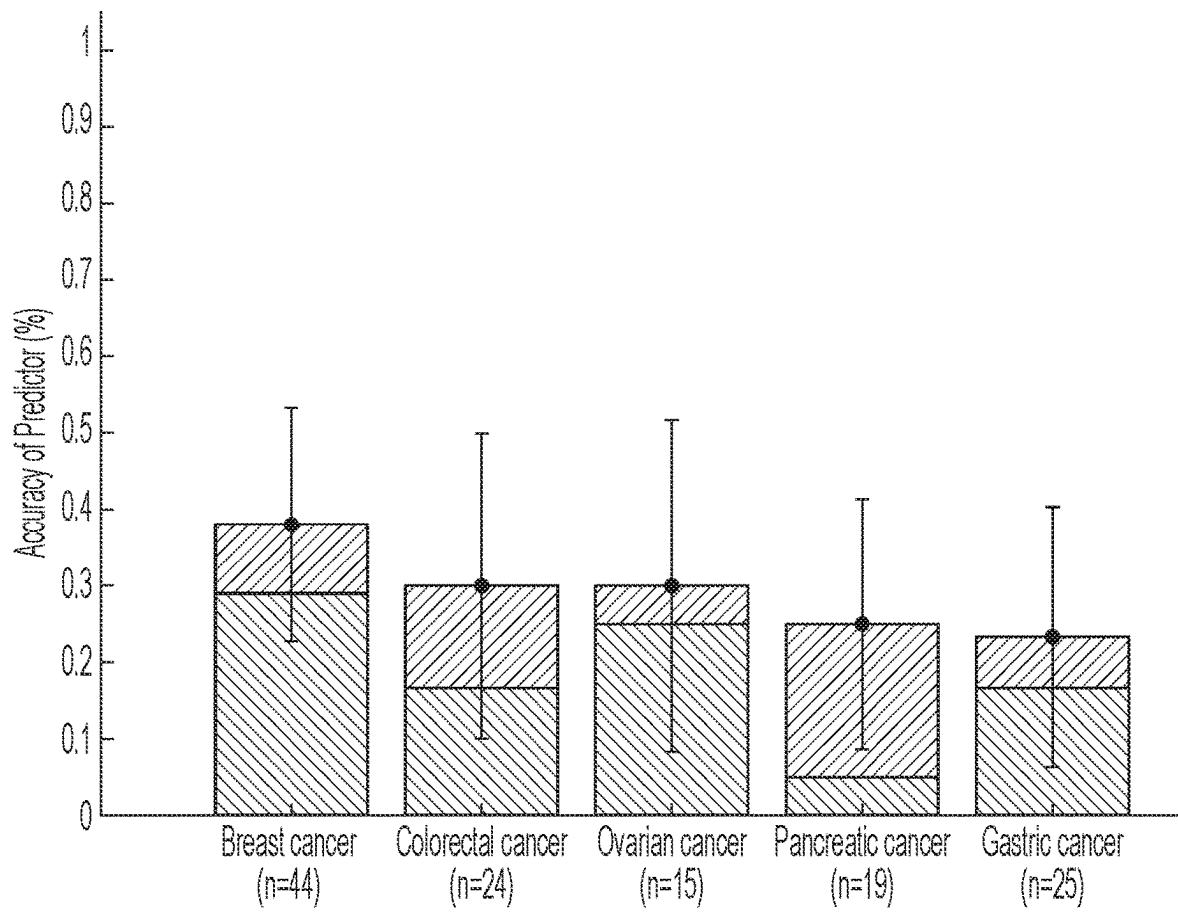


FIG. S21

**DE NOVO CHARACTERIZATION OF
CELL-FREE DNA FRAGMENTATION
HOTSPOTS IN HEALTHY AND
EARLY-STAGE CANCERS**

**CROSS REFERENCE TO RELATED
APPLICATIONS**

[0001] The current application claims priority to U.S. provisional applications Ser. No. 63/042,116, filed Jun. 22, 2020 and Ser. No. 63/051,752, filed Jul. 14, 2020, the entire disclosures of which are incorporated herein by reference.

BACKGROUND

[0002] Circulating cell-free DNA (cfDNA) from patients' plasma is a promising non-invasive biomarker for diagnosing and screening early-stage cancers[1]. The fragmentation patterns of cfDNA are not evenly distributed in the genome and associated with the local epigenetic backgrounds[2,3]. The cfDNA fragmentation patterns are altered in cancer, bringing enormous signals from both tumor and peripheral immune cells to detect early-stage cancers[4,5]. Recently, several patterns have been derived to capture the full spectrums of the cfDNA fragmentation in cancer, such as patterns near transcription start sites (TSS) and transcription factor binding sites (TFBS), orientation-aware cfDNA fragmentation (OCF), the preferred-ended position of cfDNA, motif diversity score (MDS), large-scale fragmentation patterns at mega-base level (DELFI), and nucleosome positioning (window protection score, WPS)[3,4,6-10]. However, the studies of fragmentation patterns at selected known regulatory elements, such as TSS[6], TFBS[9], and known open chromatin regions in immune cells (OCF)[8], limited their opportunities to unbiasedly characterize the genome-wide fragmentation aberrations on other regulatory regions in early-stage cancers. The preferred-ended position of cfDNA has not been associated with known gene-regulatory elements yet[7]. MDS[10] is a single summary statistic score for each patient that does not allow further explorations of its association with specific gene-regulatory elements. The large-scale fragmentation patterns at mega-bases level (DELFI)[4] are challenging to be associated with the fine-scale gene-regulatory elements, genes, pathways, and therefore further druggable targets for the interventions of early-stage cancers. These challenges limited their potential opportunity to characterize the underlying unknown gene-regulatory aberrations during the initiations of early-stage cancers.

[0003] To conquer these challenges, an unbiased genome-wide approach is needed to narrow down the regions of interest from cfDNA fragments directly. A previous study on cfDNA from healthy and late-stage cancers de novo characterize the regions with high WPS signals that are associated with nucleosome occupancies[3]. Nucleosome occupancies inside the cells are usually measured by MNase-seq, which is not comprehensively performed at various primary cell types across different human pathological conditions, such as cancer. Thus, the characterization of nucleosome occupied regions from cfDNA will still limit our scope to dissect the potential regulatory aberrations in cancer. However, reduced fragmentation process ("fragmentation cold-spots") at nucleosome-occupied regions, on the other side, indicates the potential existence of increased fragmentation process ("fragmentation hotspots") at the open chromatin

regions. Open chromatin regions have recently been comprehensively profiled by ATAC-seq and DNase-seq at many primary cell types across different physiological conditions, including cancer and immune cells[11,12]. Transcription factors usually bind the open chromatin regions rather than the nucleosome occupied regions[13]. Moreover, non-coding genetic variants associated with different complex diseases are enriched in the open chromatin regions from related cell types[14-16]. Therefore, instead of identifying "fragmentation coldspots" at nucleosome-occupied regions, we hypothesize that the characterization of cfDNA "fragmentation hotspots" at open chromatin regions will not only boost the power for the identification of nuanced pathological conditions, such as early-stage cancer, but also elucidate the unknown gene-regulatory mechanisms indicated by the fragmentation patterns from patients' plasma cfDNA.

SUMMARY

[0004] The current disclosure provides an approach to de novo characterize the cell-free DNA fragmentation hotspots from whole-genome sequencing. In healthy, hotspots are enriched in gene-regulatory elements, including promoters, hematopoietic-specific enhancers, and 3' end of transposons. In early-stage cancers, fragmentations are aberrant at hotspots near microsatellites, CTCF, and genes enriched in immune processes from peripheral immune cells, which indicated the aberrations of chromatin organizations and immune-gene expressions during cancer initiations. Utilizing these hotspots, we diagnosed eight early-stage cancers from two studies with high accuracy. Moreover, we identified the tissues-of-origin of multi-cancers with a median of 85% accuracy, which has not been shown by other fragmentation approaches. The results highlight the significance of de novo characterizing the cell-free DNA fragmentation hotspots for detecting early-stage cancers and dissection of gene-regulatory aberrations in cancers.

[0005] Embodiments of the current disclosure provide a computational approach, named Cell fRee dnA fraGmentation (CRAG), to de novo identify the genome-wide cfDNA fragmentation hotspots by utilizing the weighted fragment coverages from cfDNA paired-end WGS data. We analyzed the gene-regulatory potentials of these fragmentation hotspots in healthy individuals and patients with early-stage cancer, which revealed the previously unknown gene-regulatory aberrations from peripheral immune cells in cancers. Finally, we utilized these fragmentation hotspots for the detection and localization of multiple early-stage cancers.

[0006] In an aspect a method for identifying DNA fragmentation hotspots as part of diagnosing early stage cancer or certain other non-malignant disease includes steps of: de-novo characterizing genome-wide cell-free DNA fragmentation hotspots from whole-genome sequencing by integrating fragment size and coverage into a score; and identifying DNA fragmentation hotspots of interest based upon the score being below a threshold. In a further detailed embodiment, the score identifies regions with lower fragment coverage and smaller fragment size.

[0007] Alternatively, or in addition, the method further includes a step of scanning a chromosome with a sliding window of a first size and a step with a second size. In a detailed embodiment, the score is calculated by weighting fragment coverage based on a ratio of average fragment size in the sliding window versus that in the whole chromosome.

In a further detailed embodiment, the score is calculated based upon the following equation wherein, in the i_{th} window:

$$IFS_i = n_i * \left(1 + \frac{l_i}{L}\right) \quad (1)$$

$$C_i = \lfloor IFS_i \rfloor \quad (2)$$

where C_i is the IFS score round down to the nearest integer in the i_{th} window, n_i is the number of fragments whose mid-points are located within the i_{th} window, l_i is the average fragment size in the i_{th} window, L is the average fragment size in the whole chromosome.

[0008] In an embodiment, the first size is 200 bp and the second size is 20 bp.

[0009] Alternatively, or in addition, the method may include a step of utilizing identified DNA fragmentation hotspots for the detection of early-stage cancer. In a further detailed embodiment, the detection step may include performing Gene Ontology (GO) analysis of the identified DNA fragmentation hotspots, or performing Motif analysis of the identified DNA fragmentation hotspots.

[0010] In an embodiment, the integrating step weighs fragment coverages with size information. In a further detailed embodiment, the integrating step weighs the fragment coverage based on a ratio of fragment size in a window versus that in the whole chromosome.

[0011] Another aspect provides a method for identifying genomic regions with higher fragmentation rates than the local and global backgrounds as part of diagnosing early stage cancer (or certain other non-malignant disease). The method includes steps of: de-novo characterizing genome-wide cell-free DNA fragmentation regions with higher fragmentation rates than the local and global backgrounds from whole-genome sequencing by weighing the fragment coverages in each region by a ratio of average fragment sizes in the region versus that in the whole chromosome to generate a score; and identifying DNA fragmentation regions of interest based upon comparing the score with a threshold. In an embodiment, the method further includes a step of scanning a chromosome with a sliding window of a first size and a step with a second size. In a further detailed embodiment, the score is calculated by weighting fragment coverage based on a ratio of average fragment size in the sliding window versus that in the whole chromosome. Alternatively, or in addition, the first size is 200 bp and the second size is 20 bp.

[0012] In an embodiment, the method further includes utilizing identified DNA fragmentation hotspots for the detection of early-stage cancer. In a more detailed embodiment, the detection step may include performing Gene Ontology (GO) analysis of the identified DNA fragmentation hotspots; or performing Motif analysis of the identified DNA fragmentation hotspots.

[0013] These and other aspects and advantages of the current disclosure will be apparent from the following description, the appended claims and the attached drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

[0014] FIGS. 1a-d. Illustrate a schematic of an exemplary CRAG approach.

[0015] FIG. 1a. Illustrates the overall workflow for the detection and localization of early-stage cancer.

[0016] FIG. 1b. Is a schematic of hotspot identification.

[0017] FIG. 1c. Is the Q-Q plot for the negative binomial modeling of IFS score distribution.

[0018] FIG. 1d. Is the distribution of IFS around the hotspots in the BH01 dataset.

[0019] FIG. 2a-2h. Provides charts illustrating CfDNA fragmentation hotspots are enriched at gene-regulatory regions in healthy.

[0020] FIG. 2a. Is the overlap of cfDNA fragmentation hotspots and CGI Transcription Starting Sites (TSSs), non-CGI TSSs, 5' exon boundary (no TSS and CTCF within +/- 2 kb), Transcription Termination Sites (TTSSs) (no TSS and CTCF within +/- 2 kb), CTCF transcription factor binding sites (no TSS within +/- 4 kb), and random genomics regions.

[0021] FIG. 2b. Is the DNA accessibility levels from hematopoietic cells around the cfDNA fragmentation hotspots.

[0022] FIG. 2c. Is the histone modification levels from monocytes around the cfDNA fragmentation hotspots.

[0023] FIG. 2d. Is the H3K4me1 histone modification levels from hematopoietic (solid lines) and non-hematopoietic (dashed lines) cells around the cfDNA fragmentation hotspots.

[0024] FIG. 2e. Is the enrichment of hotspots at tissue-specific chromHMM states (TssA, TssFlank, and Enhancer, also overlapped with tissue-specific open chromatin regions). Odds ratio is compared with matched random regions (matched chromosome and length, repeated 10 times). Error bar is based on 95% confidence interval. P value is calculated based on Fisher exact test.

[0025] FIG. 2f. Is a ROC curve for the prediction of open chromatin regions by the linear SVM model on the IFS score and other features in the benchmark datasets.

[0026] FIG. 2g. Is the overlap of cfDNA fragmentation hotspots and 3' end of transposons (Alu, L1, and LTR)

[0027] FIG. 2h. Is the cfDNA methylation level from healthy individuals around the 3' end of Alu that overlapped or not overlapped with the cfDNA fragmentation hotspots.

[0028] FIGS. 3a-3g. Provide charts and graphs illustrating the aberrations of cfDNA fragmentation patterns at hotspots in early-stage cancers.

[0029] FIG. 3a. Is a volcano plot of z-score differences and p-value (two-way Mann-Whitney U test) for the aberration of IFS in cfDNA fragmentation hotspots between early-stage HCC and healthy.

[0030] FIG. 3b. Is unsupervised clustering on the Z-score of IFS at the top 10,000 most variable cfDNA fragmentation hotspots called from HCC and healthy samples.

[0031] FIG. 3c. Is receiver operator characteristics (ROC) for the detection of early-stage HCC by using IFS (after GC bias correction) from all the cfDNA fragmentation hotspots (red), copy number variations (brown), and mitochondrial genome copy number analysis (black).

[0032] FIG. 3d. Are scatter plots of z-score differences and feature importance (coefficient in linear SVM) split the cfDNA fragmentation hotspots into two groups: hypo-fragmented in cancer (Class I) and hyper-fragmented in cancer (Class II).

[0033] FIG. 3e. Is the fraction of Class I and Class II hotspots that are overlapped with microsatellite repeats, as well as their relative distance to the nearest TSS.

- [0034] FIG. 3*f*. Is the top 10 motif enrichment at Class I and Class II hotspots.
- [0035] FIG. 3*g*. Is the top 10 enrichment of Gene Ontology Biological Process at Class I and Class II hotspots.
- [0036] FIG. 4*a-d*. Illustrates graphs and charts for the detection and localization of multiple early-stage cancers.
- [0037] FIG. 4*a*. Is the t-SNE visualization on the Z-score of IFS (after GC bias correction) at the most variable cfDNA fragmentation hotspots (one-way ANOVA test with p value<0.01) across multiple different early-stage cancer types and healthy conditions.
- [0038] FIG. 4*b*. Is unsupervised clustering on Z-score of IFS (after GC bias correction) at the top 40,000 most variable cfDNA fragmentation hotspots across multiple different early-stage cancer types and healthy conditions.
- [0039] FIG. 4*c*. Is the sensitivity across different cancer stages at 100% specificity to distinguish cancer and healthy condition by using IFS (after GC bias correction) at cfDNA fragmentation hotspots. Error bars represent 95% confidence intervals.
- [0040] FIG. 4*d*. Is percentages of patients correctly classified by one of the two most likely types (sum of orange and blue bars) or the most likely type (blue bar). Error bars represent 95% confidence intervals.
- [0041] FIGS. S1*a-b* Represent fragmentation patterns near the cfDNA fragmentation hotspots.
- [0042] FIG. S1*a*. The distribution of IFS from IH01.
- [0043] FIG. S1*b* adjusted IFS (after k-mer correction) from BH01 around the fragmentation hotspots called at BH01 dataset.
- [0044] FIG. S2*a1-S2a12* are a representation of Genome browser tracking of cfDNA fragmentation hotspots. The first box is near promoter regions. The second box is at intergenic regions.
- [0045] FIG. S3 is a graph presenting the enrichment of ATAC-seee signals from neutrophils around the cfDNA fragmentation hotspots (BH01).
- [0046] FIGS. S4*a-b* provide graphs illustrating epigenetic signals around cfDNA fragmentation hotspots (BH01).
- [0047] FIG. S4*a*. The histone modification signal distributions (-log 10 P-value calculated by MACS2, downloaded from Roadmap Epigenomics Consortium) from neutrophil, B cell, and T cell around cfDNA fragmentation hotspots (BH01).
- [0048] FIG. S4*b*. The enrichment of cfDNA hotspots from BH01 at tissues-specific chromHMM states (TssA, Tss-Flank, and Enhancer). The odds ratio is compared with matched random regions (matched chromosome and length, repeated 10 times). Error bar is based on the 95% confidence interval. P-value is calculated based on Fisher's exact test. BH01 cfDNA fragmentation hotspots are identified from GC-bias corrected IFS signals.
- [0049] FIG. S5 provides a boxplot of the conservation score (PhastCons) within cfDNA fragmentation hotspots and matched random regions.
- [0050] FIG. S6*a-c*. Illustrates CfDNA fragmentation hotspots and transposable elements (TE).
- [0051] FIG. S6*a*. Is the mappability score distribution at 3' end of TE.
- [0052] FIG. S6*b*. Is the G+C % content distribution at 3' end of TE.
- [0053] FIG. S6*c*. The top 10 motif enrichment at hotspots after the 3' end of TE.
- [0054] FIG. S7 provides a graph illustrating the power estimation for the cfDNA fragmentation hotspots called by CRAG with different numbers of fragments.
- [0055] FIG. S8. Illustrates unsupervised clustering on the Z-score of IFS at the top 10,000 most variable cfDNA fragmentation hotspots called from HCC and healthy samples (after GC bias correction).
- [0056] FIGS. S9*a-e*. Illustrates unsupervised clustering on the Z-score of IFS at the most variable cfDNA fragmentation hotspots called from HCC and healthy samples.
- [0057] FIG. S9*a*. Clustering on the euclidean distance metrics from the top 10,000 most variable hotspots.
- [0058] FIG. S9*b*. Clustering on the spearman correlation distance metrics from the top 20,000 most variable hotspots.
- [0059] FIG. S9*c*. Clustering on the euclidean distance metrics from the top 20,000 most variable hotspots.
- [0060] FIG. S9*d*. Clustering on the spearman correlation distance metrics from the top 30,000 most variable hotspots.
- [0061] FIG. S9*e*. Clustering on the euclidean distance metrics from the top 30,000 most variable hotspots.
- [0062] FIGS. S10*a-b*. Provides graphs illustrating receiver operator characteristics (ROC) for the detection of early-stage HCC.
- [0063] FIG. S10*a*. IFS from cfDNA fragmentation hotspots (after GC bias correction) and,
- [0064] FIG. S10*b*. Using IFS signals but with different machine learning approaches.
- [0065] FIGS. S11*a-b*. Provides charts illustrating the functional analysis of Class I hotspot and Class II hotspots in HCC and healthy controls.
- [0066] FIG. S11*a*. The enrichment of silenced genes in PBMC (promoters are overlapped with Class I hotspots) from early-stage HCC comparing to that from healthy controls.
- [0067] FIG. S11*b*. The cfDNA methylation level is significantly lower at HCC comparing to healthy controls in Class II hotspots (also overlapped with microsatellites).
- [0068] FIG. S12*a-c*. Provides plots illustrating Principal Component Analysis (PCA) on the cfDNA fragmentation hotspots. PCA analysis on Z-score transformed IFS signals from
- [0069] FIG. S12*a*. All hotspots from pooled HCC (red), chronic HBV infection (cyan), HBV-associated liver cirrhosis (green), and Healthy (blue) samples.
- [0070] FIG. S12*b*. Matched random regions (matched chromosome and length with hotspots) from pooled HCC (red), chronic HBV infection (cyan), HBV-associated liver cirrhosis (green), and Healthy (blue) samples.
- [0071] FIG. S12*c*. All hotspots from pooled random grouped samples, the sample sizes are matched with HCC, chronic HBV infection, HBV-associated liver cirrhosis, and Healthy.
- [0072] FIG. S13. Illustrates unsupervised clustering on the Z-score of IFS at the top 10,000 most variable cfDNA fragmentation hotspots called from HCC (red), chronic HBV infection (cyan), HBV-associated liver cirrhosis (green), and Healthy (blue) samples (a). Before and (b). After GC bias correction.
- [0073] FIG. S14*a-i*. Illustrates unsupervised clustering on the Z-score of IFS at the most variable cfDNA fragmentation hotspots called from HCC, HBV-associated liver cirrhosis, chronic HBV infection, and healthy individuals. \
- [0074] FIG. S14*a*. Clustering on the euclidean distance metrics from the top 30,000 most variable hotspots.

- [0075] FIG. S14*b*. Clustering on the spearman correlation distance metrics from the top 10,000 most variable hotspots.
- [0076] FIG. S14*c*. Clustering on the euclidean distance metrics from the top 10,000 most variable hotspots.
- [0077] FIG. S14*d*. Clustering on the spearman correlation distance metrics from the top 20,000 most variable hotspots.
- [0078] FIG. S14*e*. Clustering on the euclidean distance metrics from the top 20,000 most variable hotspots.
- [0079] FIG. S14*f*. Clustering on the spearman correlation distance metrics from the top 40,000 most variable hotspots.
- [0080] FIG. S14*g*. Clustering on the euclidean distance metrics from the top 40,000 most variable hotspots.
- [0081] FIG. S14*h*. Clustering on the spearman correlation distance metrics from the top 50,000 most variable hotspots.
- [0082] FIG. S14 *i*. Clustering on the euclidean distance metrics from the top 50,000 most variable hotspots.
- [0083] FIG. S15*a-b*. Provides graphs representing receiver operator characteristics (ROC) to distinguish early-stage HCC with benign conditions (HBV-associated liver cirrhosis and chronic HBV infection) by using IFS from cfDNA fragmentation hotspots
- [0084] FIG. S15*a*. Before GC bias correction.
- [0085] FIG. S15*b*. After GC bias correction.
- [0086] FIG. S16*a-c*. Illustrates the aberrations of IFS (before GC bias correction) across multiple early-stage cancer and healthy.
- [0087] FIG. S16*a*. t-SNE visualization on the Z-score of IFS (before GC bias correction) at the top 40,000 most variable cfDNA fragmentation hotspots across multiple different early-stage cancer types and healthy.
- [0088] FIG. S16*b*. Unsupervised clustering (WPGMA method on spearman correlation distance) on Z-score of IFS (before GC bias correction) at the top 40,000 most variable cfDNA fragmentation hotspots across multiple different early-stage cancer types and healthy.
- [0089] FIG. S16*c*. Unsupervised clustering (Ward's method on euclidean distance) on Z-score of IFS (before GC bias correction) at the top 40,000 most variable cfDNA fragmentation hotspots across multiple different early-stage cancer types and healthy.
- [0090] FIG. S17*a-g*. Provides graphs illustrating receiver operator characteristics (ROC) for the detection of different early-stage cancers by using IFS from cfDNA fragmentation hotspots before (left panel) and after (right panel) GC bias correction.
- [0091] FIG. S17*a*. Breast cancer.
- [0092] FIG. S17*b*. Colorectal cancer.
- [0093] FIG. S17*c*. Ovarian cancer.
- [0094] FIG. S17*d*. Gastric cancer.
- [0095] FIG. S17*e*. Lung cancer.
- [0096] FIG. S17*f*. Pancreatic cancer.
- [0097] FIG. S17*g*. Bile duct cancer.
- [0098] FIG. S18*a-g*. Provides bar graphs illustrating the sensitivity across different cancer stages at 100% specificity for the detection of different early-stage cancers by using IFS from cfDNA fragmentation hotspots before (left panel) and after (right panel) GC bias correction. The sample size in each stage is at the bottom of each bar.
- [0099] FIG. S18*a*. Breast cancer.
- [0100] FIG. S18*b*. Colorectal cancer.
- [0101] FIG. S18*c*. Ovarian cancer.
- [0102] FIG. S18*d*. Gastric cancer.
- [0103] FIG. S18*e*. Lung cancer.
- [0104] FIG. S18*f*. Pancreatic cancer.

[0105] FIG. S18*g*. Bile duct cancer. Error bars represent 95% confidence intervals.

[0106] FIG. S19*a-b*. Provides bar graphs illustrating the sensitivity at 100% specificity for the detection of early-stage cancer across different tumor fractions.

[0107] FIG. S19*a*. Cristiano et al. data and

[0108] FIG. S19*b*. HCC vs. Healthy at Jiang et al. data. The tumor fraction is estimated by ichorCNA.

[0109] FIG. S20 Provides a bar graph illustrating tissues-of-origin prediction across six different cancer types. Percentages of patients correctly classified by one of the two most likely types (sum of orange and blue bars) or the most likely type (blue bar). Error bars represent 95% confidence intervals.

[0110] FIG. S21. Provides a bar graph illustrating tissues-of-origin prediction randomly by sample frequency across five cancer types. Percentages of patients correctly classified by one of the two most likely types (sum of orange and blue bars) or the most likely type (blue bar). Error bars represent 95% confidence intervals.

DETAILED DESCRIPTION

CRAG: A Probabilistic Model to Characterize the Cell-Free DNA Fragmentation Hotspots.

[0111] Embodiments of the current disclosure provide a computational approach to de novo characterize the fine-scale genomic regions with higher fragmentation rates than the local and global backgrounds, defined as cfDNA fragmentation hotspots (FIG. 1*a-b*). Since both fragment coverages and sizes are essential parts of evaluating the fragmentation process, we weighed the fragment coverages in each region by the ratio of average fragment sizes in the region versus that in the whole chromosome, named integrated fragmentation score (IFS) (Details in Methods). The negative binomial model we provided correctly captured the variation of IFS in the background and indicated the existence of cfDNA fragmentation hotspots (FIG. 1*c*, Details in Methods). Since sequencing coverages are usually affected by the G+C % content, we also normalized the IFS signals with the G+C % content within the regions (Details in Methods). We used the cfDNA deep WGS data (BH01, ~100×)[3] from the healthy non-pregnant individuals as the primary data set to evaluate our approach in healthy individuals. In the BH01 dataset, we identified 277,109 cfDNA fragmentation hotspots. The IFS distributions in both BH01 and another independent dataset from a healthy individual (IH01, ~100×) showed expected depletions at the center of BH01 hotspots (FIG. 1*d*, FIG. S1a).

[0112] Further, we normalized the IFS signals by k-mer composition (n=2) at BH01 hotspots (Details in Methods). We did not observe any change in the overall distribution of fragmentation patterns before and after the correction (FIG. S1*b*). These results suggested that our model robustly captured the cfDNA fragmentation hotspots in healthy individuals.

Cell-Free DNA Fragmentation Hotspots are Highly Enriched in Gene-Regulatory Elements.

[0113] We next sought to characterize the genomic distributions of these fragmentation hotspots in healthy individuals (BH01). Similar to the previous studies on the open chromatin regions[17], the fragmentation hotspots are

highly enriched at the CpG island (CGI) promoters and CTCF insulators, but not enriched at the non-CGI promoters, 5' exon boundaries, transcription terminated sites (TTS), and random genomic regions (FIG. 2a). Since hematopoietic cells are the major contributors to cfDNA in healthy non-pregnant individuals[18], we plotted the distributions of DNA accessibility signals measured by different platforms at the major hematopoietic cell types in peripheral blood around the hotspots. We found the high enrichment patterns as expected (FIG. 2b, FIG. S2, FIG. S3). Also, we observed the high enrichment of active histone marks, such as H3K4me3 and H3K27ac. We found the depletion of repressive histone marks, such as H3K27me3, H3K9me3, as well as the gene-body histone mark H3K36me3. The enhancer mark H3K4me1, from hematopoietic cell types but not other cell types, showed the high enrichment around the hotspots (FIG. 2c-d, FIG. S2, FIG. S4a). To further understand the enrichment of fragmentation hotspots at different chromatin states, we utilized the 15-states chromHMM segmentation results across different cell types from the NIH Roadmap Epigenomics Mapping Consortium[19]. The hotspots mainly showed the enrichment in the tissue/cell-type-specific chromHMM states from hematopoietic cell types but not other cell types. (FIG. 2e, FIG. S4b). The evolutionary conservation score (phastCons) in hotspots is also significantly higher than matched random regions (two-sided Mann-Whitney U test, $p < 2.2 \times 10^{-16}$, FIG. S5)[20]. Finally, we utilized the constitutively active regions and repressive

regions to benchmark the efficiency that we can detect the open chromatin regions by the fragmentation score, we achieved the 0.92 area under the curve (AUC) to predict the known open chromatin regions (FIG. 2f, Details in Methods).

[0114] To explore the unknown regulatory potentials of cfDNA fragmentation hotspots, we collected 523 public available open chromatin region datasets measured by DNase-seq or ATAC-seq across different cell types (Details in Table S1). These cell types are the major known contributors to cfDNA in healthy non-pregnant individuals, including liver and rest or activated immune cells from the Roadmap Epigenomics Consortium, ENCODE, BLUEPRINT, and other publications[12,19,21-23]. Interestingly, after excluding the potential overlap with these known open chromatin regions, we noticed a high enrichment of hotspots not within but right after the 3' end of transposable elements (TEs), which are not the regions with the low mappability and high G+C % bias (FIG. 2g, FIG. S6a,b). The motif enrichment results at these hotspots right after the 3' end of TEs further suggested the high enrichment of pioneer transcription factors, such as OCT (POU, Homeobox), which usually bind the nucleosome occupied regions (FIG. S6c) [24]. Moreover, we observed the differences of DNA methylation at the same regions (right after the 3' end of Alu) with or without the overlap of hotspots, which indicates the potential functional association between hotspots and the local epigenetic status after the 3' end of TEs (FIG. 2h).

TABLE S1

Table S1: list of public data we used

Access id	cell type	assay type	publication	URL
gene annotation, including TSS/exon (Genecode Release 30, GRCh37, Comprehensive gene annotation) CTCF motif (hg19)			"Suresh Cuddapah et al." "Global Analysis of the Insulator Binding Protein CTCF in Chromatin Barrier Regions Reveals Demarcation of Active and Repressive Domains"."	https://www.gencodegenes.org/human/release_30lift37.html
.2009 January; 19(1): 24-32. doi: 10.1101/gr.082800.108. Epub 2008 Dec. 3" CpG island (UCSC Table browser) repeats (hg19, RepeatMasker from UCSC table browser)			"Suresh Cuddapah et al." "Global Analysis of the Insulator Binding Protein CTCF in Chromatin Barrier Regions Reveals Demarcation of Active and Repressive Domains"."	https://genome.ucsc.edu/cgi-bin/hgTables https://genome.ucsc.edu/cgi-bin/hgTables
GC contents			Smit AFA, Hubley R, Green P. RepeatMasker Open-3.0. http://www.repeatmasker.org.1996-2010.org	http://hgdownload.cse.ucsc.edu/goldenPath/hg19/gc5Base/ https://genome.ucsc.edu/cgi-bin/hgTables
Dark regions (merged wgEncodeDacMapability ConsensusExcludable and wgEncodeDukeMapabilityRegionsExcludable in hg19)				

TABLE S1-continued

Table S1: list of public data we used				
Access id	cell type	assay type	publication	URL
"phastCons scores for multiple alignments of 99 vertebrate genomes to the human genome(hg19)"			"Siepel A, Bejerano G, Pedersen J S, Hinrichs A S, Hou M, Rosenbloom K, Clawson	
H, Spieth J, Hillier L W, Richards S, et al. Evolutionarily conserved elements in vertebrate, insect, worm, and yeast genomes. <i>Genome Res.</i> 2005 August; 15(8): 1034-50. (http://www.genome.org/cgi/doi/10.1101/gr.3715005)				
Merged data from 32 healthy controls (EGAS00001001219)	Human healthy plasma	whole-genome bisulfite sequencing data	Sun et al. 2015 PNAS. https://doi.org/10.1073/pnas.1508736112	
cfdNA WGBS data from early-stage HCC and healthy controls (EGAS00001000566)	Human plasma from HCC and healthy	whole-genome bisulfite sequencing data	Chan et al. 2013 PNAS. https://doi.org/10.1073/pnas.1313995110	
Gene expression data in PBMC from early-stage HCC and healthy controls SRR2129993 (BH01) (SRA)	PBMC	gene expression microarray	Shi et al. 2014 Eur J Cancer. https://doi.org/10.1016/j.ejca.2013.11.026	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE49515
SRR2130050 (IH01) (SRA)	Human healthy plasma	whole-genome sequencing data (Illumina HiSeq 2000)	Snyder M W, Kircher M, Hill A J, Daza R M et al. Cell-free DNA Comprises an In Vivo Nucleosome Footprint that Informs Its Tissues-Of-Origin. Cell 2016 Jan. 14; 164(1-2): 57-68. PMID: 26771485	https://trace.ncbi.nlm.nih.gov/Traces/sra/?run=SRR2129993
SRR2130050 (IH02) (SRA)	Human healthy plasma	whole-genome sequencing data (Illumina HiSeq 2000)	Snyder M W, Kircher M, Hill A J, Daza R M et al. Cell-free DNA Comprises an In Vivo Nucleosome Footprint that Informs Its Tissues-Of-Origin. Cell 2016 Jan. 14; 164(1-2): 57-68. PMID: 26771486	https://trace.ncbi.nlm.nih.gov/Traces/sra/?run=SRR2130050

TABLE S1-continued

Table S1: list of public data we used				
Access id	cell type	assay type	publication	URL
225 samples from PNAS paper(32 healthy samples, 90 HCC samples, 67 HBV samples and 36 Cirrhosis samples)	Human plasma	whole-genome sequencing	Jiang P, Chan C W M, Chan K C A, et al. Lengthening and shortening of (Illumina HiSeq 2000) plasma DNA in hepatocellular carcinoma patients[J]. Proceedings of the National Academy of Sciences, 2015, 112(11): E1317-E1325.	
423 samples from Nature paper (215 healthy samples, 208 cancer samples (54 breast cancer samples, 26 bile duct samples, 27 colorectal cancer samples, 27 gastric samples, 12 lung cancer samples, 28 ovarian cancer samples and 34 pancreatic samples))	Human plasma	whole-genome sequencing	Cristiano S, Leal A, Phallen J, et al. Genome-wide cell-free DNA fragmentation in patients with cancer[J]. Nature, 2019, 570(7761): 385-389.	
196 peaks from 96 different samples (BLUEPRINT)	White blood cells	DNase-Seq		http://dcc.blueprint-epigenome.eu/#/files
14 peaks (narrow peaks and broad peaks) from 7 samples (E29, E32, E33, E34, E46, E50, E51) (Roadmap)	White blood cells	DNase-Seq	Bernstein B E, Stamatoyannopoulos J A, Costello J F, et al. The NIH roadmap epigenomics mapping consortium[J]. Nature biotechnology, 2010, 28(10): 1045-1048.	https://egg2.wustl.edu/roadmap/data/byFileType/peaks/consolidated/
GSE118189 (NCBI)	25 blood cell types	ATAC-Seq	Diego Calderon, Michella L. T. Nguyen, Anja Mezger, Arwa Kathiria, Vinh Nguyen, Ninnia Lescano, Beijing Wu, John Trombetta, Jessica V. Ribado, David A. Knowles, Ziyue Gao, Audrey V. Parent, Trevor D. Burt, Mark S. Anderson, Lindsey A. Criswell, William J. Greenleaf, Alexander Marson, and Jonathan K. Pritchard. Landscape of stimulation-responsive chromatin across diverse human immune cells. bioRxiv 409722; doi: 10.1101/409722	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE118189
GSE74912 (NCBI)	hematopoietic and leukemic cell types	ATAC-Seq	Corces M R, Buenrostro J D, Wu B, Greenside PG et al. Lineage-	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSE74912

TABLE S1-continued

Table S1: list of public data we used				
Access id	cell type	assay type	publication	URL
ENCF0461VKA and ENCF081JVT (ENCODE)	liver feat	DNase-Seq	specific and single-cell chromatin accessibility charts human hematopoiesis and leukemia evolution. Nat Genet 2016 October; 48(10): 1193-203. PMID: 27526324	https://www.encodeproject.org/experiments/ENC562FNN/
GSM2400294 (Both board peaks and narrow peaks: NCBI)	<i>Homo sapiens</i> right lobe of liver tissue female adult	DNase-Seq		https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSM2400294
ENCF957JFJ and ENCF571RHF (ENcode)	<i>Homo sapiens</i> HepG2	DNase-Seq		https://www.encodeproject.org/experiments/ENC500EJV/
E29 (macs2 -log10 p value signal files from Roadmap)	Primary monocytes from peripheral blood	DNase-Seq (signals), H3K4me1, H3K4me3, H3K9me3, H3K27me3, H3K36me3, H3K27ac		https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/macs2signal/pval/
E30 (macs2 -log10 p value signal files from Roadmap)	Primary neutrophils from peripheral blood	DNase-Seq (signals, imputed data), H3K4me1, H3K4me3, H3K9me3, H3K27me3, H3K36me3, H3K27ac (imputed data)		https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/Imputed/DNase/E030-DNase.imputed.pval.signal.bigwig; https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/Imputed/H3K27ac/E030-H3K27ac.imputed.pval.signal.bigwig
E32 (macs2 -log10 p value signal files from Roadmap)	Primary B cells from peripheral blood	DNase-Seq (signals), H3K4me1, H3K4me3, H3K9me3, H3K27me3, H3K36me3, H3K27ac		https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/macs2signal/pval/
E34 (macs2 -log10 p value signal files from Roadmap)	Primary T cells from peripheral blood	DNase-Seq (signals), H3K4me1, H3K4me3, H3K9me3, H3K27me3, H3K36me3, H3K27ac		https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/macs2signal/pval/
E71 (macs2 -log10 p value signal files from Roadmap)	Brain hippocampus	H3K4me1, H3K4me3, H3K9me3, H3K27me3, H3K36me3, H3K27ac		https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/macs2signal/pval/
E03 (macs2 -log10 p value signal files from Roadmap)	H1 Cell Line	H3K4me1	Roadmap	https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/macs2signal/pval/ E003-H3K4me1.pval.signal.bigwig
E08 (macs2 -log10 p value signal files from Roadmap)	H9 Cell Line	H3K4me1	Roadmap	https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/macs2signal/pval/ E009-H3K4me1.pval.signal.bigwig

TABLE S1-continued

Table S1: list of public data we used				
Access id	cell type	assay type	publication	URL
E27 (macs2 -log10 p value signal files from Roadmap)	Breast Myoepithelial Primary Cells	H3K4me2	Roadmap	https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/macs2signal/pval/E027-H3K4me1.pval.signal.bigwig
E76 (macs2 -log10 p value signal files from Roadmap)	Colon Smooth Muscle	H3K4me1	Roadmap	https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/macs2signal/pval/E076-H3K4me1.pval.signal.bigwig
E96 (macs2 -log10 p value signal files from Roadmap)	Lung	H3K4me1	Roadmap	https://egg2.wustl.edu/roadmap/data/byFileType/signal/consolidated/macs2signal/pval/E096-H3K4me1.pval.signal.bigwig
43_Hm05_BIMa_Ct	Macrophages	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63215.DEEP.43_Hm05_BIMa_Ct.NOMe-Sq.accessibility_profile.bigWig
43_Hm05_BIMa_TE	Macrophages	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63235.DEEP.43_Hm05_BIMa_TE.NOMe-Sq.accessibility_profile.bigWig
43_Hm05_BIMa_TO	Macrophages	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63255.DEEP.43_Hm05_BIMa_TO.NOMe-Sq.accessibility_profile.bigWig
43_Hm05_BIMo_Ct	Monocytes	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63275.DEEP.43_Hm05_BIMo_Ct.NOMe-Sq.accessibility_profile.bigWig
51_Hf01_BICM_Ct	Central memory T-cells	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63295.DEEP.51_Hf01_BICM_Ct.NOMe-Sq.accessibility_profile.bigWig
51_Hf03_BICM_Ct	Central memory T-cells	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63339.DEEP.51_Hf03_BICM_Ct.NOMe-Sq.accessibility_profile.bigWig
51_Hf03_BIEM_Ct	Effector memory T-cells	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63348.DEEP.51_Hf03_BIEM_Ct.NOMe-Sq.accessibility_profile.bigWig
51_Hf03_BITN_Ct	Naive T-cells	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63359.DEEP.51_Hf03_BITN_Ct.NOMe-Sq.accessibility_profile.bigWig
51_Hf04_BICM_Ct	Central memory T-cells	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63381.DEEP.51_Hf04_BICM_Ct.NOMe-Sq.accessibility_profile.bigWig
51_Hf04_BIEM_Ct	Effector memory T-cells	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63401.DEEP.51_Hf04_BIEM_Ct.NOMe-Sq.accessibility_profile.bigWig
51_Hf04_BITN_Ct	Naive T-cells	NOMe-seq	DEEP	https://epigenomesportal.ca/tracks/DEEP/hg19/63433.DEEP.51_Hf04_BITN_Ct.NOMe-Sq.accessibility_profile.bigWig
GSM1972155 (NCBI GEO)	human neutrophil	ATAC-See	Chen X, Shen Y, Draper W, Buenrostro J D et al. ATAC-see reveals the accessible genome by transposase-mediated imaging and sequencing. Nat Methods 2016 December; 13(12): 1013-1020. PMID: 27749837	https://www.ncbi.nlm.nih.gov/geo/query/acc.cgi?acc=GSM1972155

TABLE S1-continued

Table S1: list of public data we used				
Access id	cell type	assay type	publication	URL
HG00096 (1000 Genomes)		whole-genome sequencing data	1000 Genomes Project Consortium. A global reference for human genetic variation[J]. Nature, 2015, 526(7571): 68-74.	ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/phase3/data/HG00096/alignment/HG00096.mapped.ILLUMINA.bwa.GBR.low_coverage.20120522.bam
HG00097 (1000 Genomes)		whole-genome sequencing data	1000 Genomes Project Consortium. A global reference for human genetic variation[J]. Nature, 2015, 526(7571): 68-74.	ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/phase3/data/HG00097/alignment/HG00097.mapped.ILLUMINA.bwa.GBR.low_coverage.20130415.bam
HG00099 (1000 Genomes)		whole-genome sequencing data	1000 Genomes Project Consortium. A global reference for human genetic variation[J]. Nature, 2015, 526(7571): 68-74.	ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/phase3/data/HG00099/alignment/HG00099.mapped.ILLUMINA.bwa.GBR.low_coverage.20130415.bam
HG00100 (1000 Genomes)		whole-genome sequencing data	1000 Genomes Project Consortium. A global reference for human genetic variation[J]. Nature, 2015, 526(7571): 68-74.	ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/phase3/data/HG00100/alignment/HG00100.mapped.ILLUMINA.bwa.GBR.low_coverage.20130415.bam
HG00101 (1000 Genomes)		whole-genome sequencing data	1000 Genomes Project Consortium. A global reference for human genetic variation[J]. Nature, 2015, 526(7571): 68-74.	ftp://ftp.1000genomes.ebi.ac.uk/vol1/ftp/phase3/data/HG00101/alignment/HG00101.mapped.ILLUMINA.bwa.GBR.low_coverage.20130415.bam
Chromatin state data (Core 15-state chromHMM model) of 44 cell types (Roadmap)				https://egg2.wustl.edu/roadmap/data/byFileType/chromhmmSegmentations/ChmmModels/coreMarks/jointModel/final/

[0115] Taken together, in healthy individuals, these de novo characterized cfDNA fragmentation hotspots are highly enriched in the gene-regulatory elements.

Cell-Free DNA Fragmentation Hotspots Reveal the Potential Regulatory Aberrations of Microsatellites, CTCF, and Genes from Peripheral Immune Cells in Early-Stage Cancer.

[0116] Further, characterized the cfDNA fragmentation hotspots in early-stage cancer. We collected the publicly available low-coverage cfDNA WGS ($\sim 1 \times$ /sample) from 90 patients with early-stage hepatocellular carcinoma (HCC, 85 of them are Barcelona Clinic Liver Cancer stage A, 5 of them are stage B) and 32 healthy individuals from the same study[25]. We pooled the low-coverage cfDNA WGS to obtain enough fragments for the hotspot calling in each condition (≥ 400 million fragments, Details in Supplementary Methods, FIG. S7)[25]. The volcano plot of the p-value (two-sample t-test) and z-score difference of IFS between HCC and healthy across all the fragmentation hotspots

showed more fractions of hypo-fragmented hotspots in early-stage HCC (FIG. 3a). Further, the unsupervised hierarchical clustering of the top 10,000 most variable hotspots showed a clear fragmentation dynamic between HCC and healthy (FIG. 3b, FIG. S8-9). Therefore, we utilized the IFS from the cfDNA fragmentation hotspots to classify the HCC and healthy individuals by a linear Support Vector Machine (SVM) approach (Details in Methods). By 10-fold cross-validation, we observed a much higher classification performance (93% sensitivity at 100% specificity) than that by using copy number variations (CNVs) with the same machine learning infrastructure and same data split (44% sensitivity at 100% specificity), mitochondria DNA (mtDNA)[25] (53% sensitivity at 100% specificity) (FIG. 3c, Table S2-3, FIG. S10a) and other previously developed fragmentation approaches [8,10,25]. We also applied other machine learning approaches with the same data split in cross-validation and observed overall good performances by using cfDNA fragmentation hotspots (FIG. S10b).

TABLE S2

Table S2: Performance comparison in HCC vs. healthy (before GC bias correction)				
	Sensitivity @100% specificity	Sensitivity @98% specificity	Sensitivity @95% specificity	Sensitivity @85% specificity
AUC				
IFS	0.9815 (0.95 CI: 0.9592-1.0000)	0.9333 (0.95 CI: 0.8462-1.0000)	0.9333 (0.95 CI: 0.8462-1.0000)	0.9333 (0.95 CI: 0.8462-1.0000)
hotspots				
CNV	0.6889 (0.95 CI: 0.5997-0.7781)	0.4444 (0.95 CI: 0.2888-0.6001)	0.6556 (0.95 CI: 0.5532-0.7580)	0.6556 (0.95 CI: 0.5532-0.7580)
mtDNA	0.9358 (0.95 CI: 0.8670-1.0000)	0.5333 (0.95 CI: 0.7274-1.0000)	0.5333 (0.95 CI: 0.7274-1.0000)	0.7556 (0.95 CI: 0.7274-1.0000)
				0.8444 (0.95 CI: 0.7274-1.0000)

TABLE S3

Table S3: Performance in in HCC vs. healthy (after GC bias correction)				
	Sensitivity @100% specificity	Sensitivity @98% specificity	Sensitivity @95% specificity	Sensitivity @85% specificity
AUC				
IFS	0.9380 (0.95 CI: 0.8670-1.0000)	0.8778 (0.95 CI: 0.7274-1.0000)	0.8778 (0.95 CI: 0.7274-1.0000)	0.8778 (0.95 CI: 0.7274-1.0000)
hotspots				

[0117] We next asked why the IFS signals in fragmentation hotspots can boost the classification performance. We split the hotspots that significantly contributed to the classification model into two groups: Class I (Hypo-fragmented in cancer) and Class II (Hyper-fragmented in cancer) (FIG. 3d, Table S4). The Class I hotspots are mostly in promoter regions, which suggests the potential silencing of genes with the decreases of fragmentation (closed chromatin status). Further, these potential silenced genes were highly enriched in the immune-related gene ontology biological processes (GO BPs) from the peripheral immune cells, such as neutrophils and myeloid cells (FIG. 3e, g, Table S5). To confirm our observations by another dataset, we collected publicly available gene expression data in peripheral blood mononuclear cells (PBMC) from early-stage HCC patients and healthy individuals[26]. The results suggested that the significant fractions of genes, whose promoters are overlapped with Class I hotspots, are indeed silenced at peripheral immune cells in early-stage HCC patients compared to the

global background (Fisher exact test, $p=1.83e^{-5}$, FIG. S11a). Class II hotspots are mostly in microsatellites, which suggested the potential increases of fragmentation at microsatellites in early-stage cancer (FIG. 3e). Since the fragmentation process is known to be affected by DNA methylation [27], to validate this observation, we collected public available cfDNA methylation data measured by whole-genome bisulfite sequencing (WGBS) in early-stage HCC patients and healthy individuals[28]. The DNA methylation level in Class II hotspots showed hypomethylation in early-stage HCC patients compared to healthy individuals, which indeed suggested the potential changes of epigenetic environments near microsatellites that can affect the cfDNA fragmentation process (FIG. S11b). We further checked the enrichment of motifs at these two groups of hotspots. The results further suggested the differences of motif enrichment between two groups (FIG. 3f). Further experimental validations from the same patients are needed to make a solid conclusion.

TABLE S4

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr1	42127500	42128620	-0.003092339	-0.745976153	-1.211270022
chr6	1536280	1536520	-0.00277068	-0.899323728	-1.274585773
chr3	131723940	131724460	-0.002745501	-0.806179554	-1.232007433
chr12	16784660	16785180	-0.002717536	-0.977168066	-1.378388792
chr7	22601680	22602140	-0.002670085	-0.801244479	-1.026692037
chr4	172758540	172759080	-0.002642817	-0.830128732	-1.279370094
chr8	117284760	117285480	0.002625112	-1.188765843	-0.755657421
chr4	62331240	62331720	-0.002595125	-0.956725388	-1.232214749
chr18	23410460	23410960	-0.002566574	-0.899173511	-1.294271456
chr8	96145560	96146820	0.002566441	-1.280740188	-0.919557716
chr12	88793740	88794100	-0.00255522	-0.900556147	-1.264688706
chr13	114004660	114005120	0.002536307	-1.179577214	-0.78345726
chr13	114004660	114005120	0.002536307	-1.179577214	-0.78345726
chr1	37633700	37634060	-0.002503515	-0.770771142	-1.190388787
chr11	115271040	115271640	-0.002498974	-0.957313931	-1.351390199

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr6	72184260	72184660	-0.002484748	-0.884544501	-1.319328215
chr17	37048940	37049440	0.002464081	-1.051891538	-0.686862085
chr11	64052060	64053720	-0.002464024	-0.811700068	-1.145782704
chr11	64052020	64053760	-0.002464024	-0.811700068	-1.145782704
chr6	40973940	40974140	0.002463092	-1.301756354	-0.9243507
chr7	129697020	129697400	-0.002441872	-0.778470013	-1.214812016
chr10	119527440	119528100	-0.002419826	-0.685792918	-1.18172942
chr14	30132100	30132480	-0.002400807	-0.723720978	-1.210908092
chr6	74819240	74819800	0.002388047	-1.192243304	-0.920509929
chr21	44189220	44190060	0.002386128	-1.042645509	-0.741092506
chr2	207831820	207832300	-0.002370527	-0.565237499	-0.992796478
chr6	80051240	80051740	-0.002359436	-0.939575187	-1.302910417
chr16	7944320	7945420	-0.00233685	-0.67910391	-1.133025032
chr11	68608180	68608820	0.002334962	-1.211278827	-0.906214929
chr9	125753080	125753300	0.002331956	-1.100666842	-0.775055031
chr9	125753080	125753300	0.002331956	-1.100666842	-0.775055031
chr3	185394240	185395300	-0.002327637	-0.885630637	-1.363697683
chr5	137617900	137618220	-0.002323105	-0.840614867	-1.21701667
chr22	40603220	40603620	-0.002314718	-0.705800753	-0.960916681
chr3	80453000	80453440	0.002312388	-1.149766375	-0.97064277
chr5	27314780	27315160	-0.002298809	-0.831072591	-1.159532797
chr22	46511940	46513160	0.0022962	-1.162368428	-0.874595747
chr1	155826720	155827260	0.002282698	-1.157656741	-0.77104378
chr6	136605060	136605500	-0.002272854	-0.843049152	-1.076637703
chr15	75339480	75339800	0.002270929	-1.099225098	-0.833808561
chr1	37633620	37634080	-0.002268608	-0.91823478	-1.289763036
chr10	63780620	63780960	-0.00226826	-0.804969567	-1.130110254
chr2	82047820	82048180	-0.002266471	-0.83849041	-1.247244194
chr2	51775780	51776260	-0.002265467	-0.898043667	-1.320142328
chr5	66748640	66749160	-0.00226123	-0.946135455	-1.24939146
chr5	84048300	84048780	-0.002253323	-0.904488238	-1.259116765
chr4	26929280	26929700	-0.002250826	-0.934122954	-1.282166847
chr3	185394260	185395300	-0.002246469	-0.930183547	-1.368360953
chr8	122389640	122389980	0.002238366	-1.09654499	-0.884019382
chr11	5707740	5707960	-0.002234188	-0.803275988	-1.149232478
chr3	45931520	45932060	-0.002233631	-0.94409477	-1.365151235
chr5	35661220	35661520	-0.002232496	-0.937511406	-1.2586665
chr1	97373480	97373940	-0.002229248	-0.843481775	-1.232304261
chr16	18092480	18092980	-0.002226695	-0.710824591	-1.082137048
chr1	113741740	113742240	-0.002222891	-0.885269605	-1.22655647
chr15	75339460	75339780	0.002216959	-1.172901618	-0.87081135
chr6	79117720	79118480	-0.002210889	-0.962347825	-1.235986073
chr1	39347780	39348380	-0.002195442	-0.765878752	-1.102433981
chr9	91056560	91056900	-0.002189466	-0.626590328	-0.966183087
chr19	16887700	16888800	0.002189206	-1.149410214	-0.819731392
chr8	138742840	138744020	0.002187092	-1.395477202	-1.067514257
chr8	138742820	138744040	0.002187092	-1.395477202	-1.067514257
chr2	73297740	73299160	0.002180218	-1.341321285	-1.080881733
chr8	117284760	117285420	0.002179818	-1.194724848	-0.819179875
chr2	17315900	17316280	-0.002176235	-0.926659875	-1.221121024
chr6	48551900	48552440	-0.002175686	-0.749641475	-1.246232536
chr1	216496380	216496860	-0.002169701	-0.682337033	-1.056119414
chr5	37517820	37518140	-0.002169195	-0.766310186	-1.146658833
chr11	41491500	41491960	0.002163609	-1.300432784	-1.156103214
chr6	72184160	72184780	-0.00216248	-0.884544501	-1.265270993
chr2	78117540	78118500	0.002161285	-1.396284482	-1.167468501
chr4	106199100	106199560	-0.002159953	-0.907672149	-1.189229624
chr10	29042340	29042780	-0.002157846	-0.810947827	-1.139366691
chr6	18092480	18092920	-0.002151984	-0.796215616	-1.192465801
chr17	73936280	73937960	0.002149503	-1.131490238	-0.827364721
chr2	112856920	112857280	-0.002148878	-0.894131991	-1.1721262
chr1	50099360	50099760	-0.002147747	-0.774491669	-1.201886556
chr15	75497040	75497460	0.002147105	-1.19613241	-0.88790135
chr22	34896000	34896840	0.002143777	-1.056089006	-0.804089504
chr6	38607280	38608160	0.002142368	-1.257980376	-0.982617816
chr22	38749080	38749580	0.002137374	-1.156192893	-0.891676471
chr13	61752060	61752560	-0.002131038	-0.932926362	-1.201013005
chr6	103306480	103306860	0.002129424	-0.956523653	-0.71096895
chr3	45931580	45932020	-0.002124758	-0.981858347	-1.388432933
chr1	108092460	108092920	0.002124736	-1.125125173	-0.984037559
chr17	2731780	2732040	0.002123727	-1.21072564	-0.84761373
chr17	2731780	2732040	0.002123727	-1.21072564	-0.84761373

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr1	98034780	98035200	-0.002123482	-0.656753725	-0.994526857
chr11	39607020	39607400	-0.002120119	-0.920310885	-1.280187263
chr1	36839460	36839780	0.00211989	-1.118065861	-0.762027957
chr1	8635440	8635820	-0.002118036	-0.813576937	-1.205300594
chr1	8635380	8635880	-0.002118036	-0.813576937	-1.205300594
chr4	34988140	34988540	-0.002115372	-0.92124435	-1.296923716
chr9	118004600	118005020	-0.002111585	-0.448055744	-0.736610843
chr5	147762720	147764120	0.00211005	-1.247801733	-0.851898823
chr1	244742000	244742280	-0.002109047	-0.680909314	-0.988903933
chr3	194338940	194339500	-0.002107397	-0.926289267	-1.297815935
chr11	74160440	74160700	0.002107094	-1.256927884	-0.980165326
chr14	44908760	44909120	-0.002105623	-0.883430947	-1.214042787
chr19	3821820	3822360	0.002100105	-1.160627889	-0.900756484
chr19	3821820	3822360	0.002100105	-1.160627889	-0.900756484
chr13	94551060	94551400	-0.00209945	-0.815797236	-1.18643113
chr13	94551000	94551460	-0.00209945	-0.815797236	-1.18643113
chr5	100423060	100423260	-0.002097332	-0.934513265	-1.241928494
chr5	100423060	100423260	-0.002097332	-0.934513265	-1.241928494
chr14	78173840	78175040	-0.002094919	-0.847999108	-1.11892702
chr8	96145520	96147040	0.002093579	-1.262956979	-0.909594362
chr20	48728900	48730520	0.002089984	-1.387785571	-1.090349593
chr1	113741780	113742180	-0.002088194	-0.949498197	-1.299581197
chr7	2387680	2387960	0.002085878	-1.038776035	-0.771693755
chr7	2387680	2387960	0.002085878	-1.038776035	-0.771693755
chr3	97947980	97948440	-0.002082591	-0.901106932	-1.183575775
chr19	39137800	39138960	0.002081556	-0.985959881	-0.747786994
chr11	114614420	114614800	-0.002079925	-0.751022389	-1.08210914
chr6	146568760	146569220	-0.002074471	-0.775337723	-1.093809409
chr9	137203080	137203600	-0.002066086	-0.77699018	-1.157180879
chr3	131723960	131724420	-0.002064998	-0.92287134	-1.250774545
chr17	46151740	46152040	0.002064131	-1.240718001	-0.973478313
chr5	17400140	17400640	-0.002063881	-0.934465823	-1.31043278
chr2	54197400	54198460	0.002062867	-1.345624484	-0.99179228
chr15	47076900	47077460	-0.002061925	-0.758983555	-1.009633926
chr2	107841300	107841800	-0.002059263	-0.886121025	-1.220164855
chr6	158552160	158552800	-0.002057233	-0.924685046	-1.323796256
chr1	6639540	6640660	0.00205701	-1.280479873	-0.948416654
chr7	118731680	118732080	0.002056879	-1.247623401	-1.067267756
chr9	130889860	130891760	0.002055939	-1.055406619	-0.774241955
chr2	232574980	232575300	0.002051518	-1.334994879	-1.084166748
chr3	10156860	10157660	0.002050067	-1.363385293	-1.124727708
chr5	99901680	99902060	-0.002046116	-1.012013458	-1.301140557
chr10	116541220	116541680	-0.002043776	-0.793209616	-1.088646672
chr1	165775680	165776040	0.002043516	-1.05608244	-0.842175134
chr4	132079620	132080200	-0.002037348	-0.900851695	-1.225720573
chr6	116851860	116852300	-0.002034477	-0.986899014	-1.297578985
chr13	101469260	101469860	-0.002031506	-1.009653953	-1.27588695
chr15	64530660	64530920	-0.002031468	-0.745286856	-1.056675893
chr17	4634000	4634260	0.00202941	-1.054332539	-0.707839773
chr4	134085840	134086480	0.002026112	-1.220803935	-1.059390095
chr7	119357280	119357640	-0.002025054	-0.966040167	-1.273312416
chr2	7302020	7302600	-0.002024059	-0.971934315	-1.306649908
chr16	80239520	80240120	-0.002022756	-0.771275912	-1.154554522
chr8	78755500	78756020	-0.002021937	-1.033161051	-1.374139334
chr4	90078060	90078620	-0.002019676	-1.025965094	-1.33098645
chr10	50356700	50357140	-0.002019618	-0.937032221	-1.256237482
chr7	20854340	20854580	-0.002014372	-0.740853496	-1.068740906
chr5	77655720	77657080	0.002013253	-1.238977299	-0.984212868
chr5	173046000	173046260	0.002008371	-1.289933021	-1.001959848
chr11	99191820	99192340	-0.002006321	-0.679196996	-1.030112001
chr12	8234640	8235100	0.002005278	-1.266577406	-0.966065513
chr9	11725700	11726280	-0.002005247	-0.714949278	-1.077955802
chr11	6494280	6495480	0.002004683	-1.230709397	-0.874896625
chr19	49630620	49631980	0.002002635	-1.132108941	-0.907694826
chr6	83953360	83953760	-0.002002063	-1.040088202	-1.355190294
chr17	6569360	6569640	0.002000028	-1.164509738	-0.86335074
chr4	168381920	168382340	-0.001994842	-0.909167318	-1.249450734
chr5	5705880	5706540	-0.00199309	-1.01918548	-1.36628835
chr2	204737760	204738340	0.001992478	-1.171952813	-1.024487387
chr8	134465300	134466180	0.001990818	-1.34156102	-1.037791619
chr19	42444160	42444780	0.001989685	-1.165497572	-0.80829194
chr1	97373520	97373920	-0.001989568	-0.875738229	-1.230132377

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr8	30890020	30891460	-0.001989522	-1.054547947	-1.253462818
chr5	88679200	88679760	-0.001988143	-0.958925903	-1.274862806
chr4	84031600	84031880	0.001988017	-1.295054845	-1.023614201
chr1	6639340	6640840	0.001987874	-1.261363323	-0.973966528
chr20	6148300	6148700	-0.001987138	-0.824094249	-1.130779993
chr8	5646740	5647120	-0.001986039	-0.796030758	-1.129834269
chr8	16046360	16046580	-0.001984397	-0.895117567	-1.14315055
chr8	16046360	16046580	-0.001984397	-0.895117567	-1.14315055
chr22	39333400	39334040	0.001984134	-1.042955385	-0.726992713
chr2	82047800	82048260	-0.001982841	-0.921720328	-1.298913832
chr11	40139400	40139960	-0.001982104	-0.795765352	-1.201999879
chr9	28584720	28585220	0.001976723	-1.180014145	-0.789915306
chr6	137182840	137183380	-0.001975408	-0.1025596874	-1.317308565
chr1	165775660	165776040	0.001974595	-1.037521689	-0.808647984
chr9	100916440	100916880	-0.001974439	-0.744073719	-1.082012409
chr4	132079600	132080240	-0.00197425	-0.9000851695	-1.219174617
chr2	207831840	207832260	-0.001971008	-0.602129851	-0.998026073
chr2	78117660	78118500	0.001967379	-1.374041701	-1.146776974
chr14	61261180	61261600	-0.001966973	-0.855090081	-1.126852743
chr14	61261140	61261640	-0.001966973	-0.855090081	-1.126852743
chr10	23039620	23040080	-0.00196649	-0.838018352	-1.138528966
chr9	134722920	134723740	0.001965861	-1.053479848	-0.676054093
chr21	16162080	16162520	-0.001964712	-0.822647934	-1.110443439
chr16	84764060	84764340	0.001964261	-1.222874216	-1.022661038
chr2	22754880	22755220	-0.00196286	-0.955837177	-1.215751512
chr2	22754820	22755280	-0.00196286	-0.955837177	-1.215751512
chr5	17400200	17400560	-0.001959929	-0.914554078	-1.28904379
chr7	91268700	91269240	-0.001959602	-1.017278731	-1.285241489
chr17	79111440	79113000	0.00195755	-1.163376165	-0.906151214
chr2	140850420	140850940	-0.001956142	-0.915955498	-1.142394718
chr17	54910600	54912420	0.001955458	-1.17984244	-0.967791609
chr1	156115800	156116080	0.001950185	-1.173452398	-0.87626236
chr6	131949040	131950040	0.001950158	-1.288198899	-0.950138449
chr1	242607780	242608200	-0.001949043	-0.89202281	-1.22619902
chr3	195923540	195923800	0.001946723	-1.314674999	-1.018986704
chr2	241505180	241505540	0.001944918	-1.232223668	-0.973024827
chr3	121553720	121554240	0.001944536	-1.405680828	-1.046155111
chr10	50213720	50214220	-0.001943715	-0.834165481	-1.152543032
chr6	66078920	66079440	-0.001942752	-0.964915561	-1.294914938
chr2	88957560	88957940	-0.001936516	-0.843589203	-1.101117282
chr11	82434860	82435300	0.001934117	-1.163791173	-0.792831769
chr13	71719800	71720360	-0.001934007	-0.872561413	-1.194090795
chr18	30509620	30509980	-0.001933271	-0.890495236	-1.162615214
chr18	30509560	30510040	-0.001933271	-0.890495236	-1.162615214
chr9	30752940	30753380	-0.001932736	-0.695371627	-1.050639567
chr19	33616820	33617100	0.001932191	-1.239927742	-0.935625328
chr10	25977260	25978140	-0.001931915	-0.976046062	-1.273276488
chr1	81729980	81730360	-0.001930942	-0.784806057	-1.135012366
chr6	134353820	134354060	-0.00193054	-0.881827394	-1.254330697
chr4	74987260	74987640	-0.001928952	-1.003049722	-1.332136807
chr19	49127000	49128180	0.0019278	-1.15336219	-0.845593144
chr14	55493360	55494280	0.001926062	-1.278830786	-1.023621205
chr5	84048320	84048720	-0.001925184	-0.996928649	-1.306033651
chr14	49502020	49502020	0.001924001	-1.196049324	-1.07740427
chr18	19180040	19181560	0.001922927	-1.359706295	-1.045293622
chr2	108579740	108580100	-0.001922199	-0.864038467	-1.167398133
chr1	32800780	32802320	0.001919181	-1.202321443	-0.991888931
chr17	75494420	75494940	0.001916279	-1.031250037	-0.801578495
chr1	235084740	235084980	-0.001912758	-0.644480109	-0.983213515
chr5	84006740	84007220	-0.0019124	-0.821731498	-1.209265769
chr1	97617860	97618420	-0.001908367	-0.784663192	-1.074576847
chr17	3795380	3796880	0.001908121	-1.165111076	-0.804202498
chr12	124046460	124046880	-0.001908049	-0.868124155	-1.151363872
chr12	124046460	124046880	-0.001908049	-0.868124155	-1.151363872
chr16	5007640	5008980	0.001907648	-1.146118674	-0.836827197
chr13	100993980	100994480	-0.001906684	-0.869523198	-1.176655713
chr9	130546680	130547080	-0.001901626	-0.676767187	-0.87632373
chr4	33132320	33132840	-0.001894859	-0.954191315	-1.288774523
chr4	134891040	134891420	-0.001894633	-0.846028503	-1.168486243
chr4	134891000	134891460	-0.001894633	-0.846028503	-1.168486243
chr1	154154740	154156460	0.001890937	-1.181963889	-0.930958681
chr22	24382040	24382420	0.001889233	-1.14981412	-0.896701558

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr21	46322340	46322680	0.001888972	-1.023318947	-0.714865189
chr5	177977980	177978400	-0.001887946	-0.932529441	-1.294480615
chr4	144079740	144080100	-0.001887937	-0.794902204	-1.154102186
chr4	144079700	144080140	-0.001887937	-0.794902204	-1.154102186
chr6	151987680	151988100	0.001886421	-1.261542839	-0.97026494
chr8	87631140	87631680	0.001883736	-1.287820352	-0.925681632
chr6	11940980	11941500	-0.001883691	-1.02359292	-1.280426423
chr8	68813600	68814080	-0.001879598	-0.889711091	-1.212107462
chr10	73571440	73572320	0.001879212	-1.183626149	-0.971472561
chr4	18741020	18741360	-0.001875019	-0.765255849	-1.100649794
chr17	39844780	39845900	0.001874206	-1.298593414	-0.965202572
chr7	68079260	68079560	-0.001872659	-0.690347762	-0.972242176
chr5	131721140	131721360	-0.001872325	-0.871628502	-1.072813992
chr10	60234520	60234880	-0.001871525	-0.904869634	-1.189110821
chr7	105939560	105939760	-0.001868739	-0.77094356	-1.00267862
chr7	105939560	105939760	-0.001868739	-0.77094356	-1.00267862
chr19	12035680	12036020	0.001866059	-1.272729988	-1.052055652
chr8	61564160	61565400	0.001865216	-1.266092102	-1.024918372
chr12	9556980	9557240	-0.001863546	-0.973206987	-1.198347579
chr7	69467860	69468420	-0.001861935	-0.900391909	-1.210527391
chr6	7723280	7723600	0.001860389	-1.214900128	-0.8853237
chr15	64890540	64891560	-0.001859852	-0.721168057	-1.037749533
chr4	110343600	110343880	0.001856663	-1.280040079	-0.953925839
chr19	12885540	12886680	0.001849991	-1.151520795	-0.929255604
chr1	229412580	229412980	-0.001849841	-0.873998841	-1.135022665
chr4	185376260	185376520	-0.001849029	-1.018481158	-1.195657154
chr19	1274680	1276140	0.001847047	-1.26757334	-1.03007361
chr22	34896000	34896860	0.001846075	-0.982958766	-0.804746927
chr7	52250580	52251000	-0.001845175	-0.898428905	-1.17046736
chr17	45776260	45776520	0.001844442	-1.221769692	-0.952590953
chr7	136713120	136713540	0.001844311	-1.077036246	-0.895811526
chr7	136713100	136713560	0.001844311	-1.077036246	-0.895811526
chr20	6787340	6787900	0.001843887	-1.149611904	-1.038027896
chr20	4434200	4434820	-0.001843462	-0.956199178	-1.321297329
chr2	108579660	108580160	-0.001841815	-0.901335835	-1.187354346
chr5	177978020	177978380	-0.001841814	-0.902175708	-1.295429063
chr16	60918560	60919180	-0.00184142	-0.891531736	-1.186688099
chr19	13215120	13215360	0.001840736	-1.080958865	-0.833853751
chr8	132693600	132694180	-0.001839751	-0.892720962	-1.21988906
chr8	1949420	1951380	-0.001839131	-1.047404973	-1.169564815
chr6	158552100	158552840	-0.001838476	-0.945421021	-1.330625834
chr2	141730340	141730780	-0.001837775	-0.869173142	-1.147677556
chr13	46502640	46503120	-0.001836885	-1.074701158	-1.353960765
chr1	166161460	166161940	-0.001836613	-0.893237371	-1.189644624
chr5	150678580	150679160	-0.001836514	-0.96139621	-1.197510092
chr1	194181540	194182080	-0.001835525	-0.810657124	-1.18916458
chr4	55903800	55904340	-0.001835414	-0.882247298	-1.257571533
chr5	88679280	88679700	-0.001830739	-0.953338366	-1.24928995
chr14	31889340	31890220	0.001829299	-1.410340596	-1.145989199
chr17	39844760	39845880	0.001826558	-1.302187753	-1.011380862
chr11	41491420	41491960	0.001826273	-1.2094448312	-1.11480952
chr21	16097140	16098160	-0.001825084	-0.865352566	-1.111299842
chr1	74663300	74664540	0.001824807	-1.156430284	-0.859660201
chr6	95667660	95668000	-0.001822732	-0.975451443	-1.247323457
chr3	3330760	3331300	-0.001821952	-1.107542754	-1.323441626
chr4	31014660	31015320	0.001821667	-1.167954076	-1.029593168
chr9	74467240	74467500	-0.001820974	-0.797071498	-1.080439763
chr2	223590580	223590820	-0.00182062	-0.890646334	-1.180985259
chr20	38816380	38816780	-0.001820484	-0.867342906	-1.160253087
chr11	33060520	33061700	0.001819249	-1.289308422	-1.042945779
chr3	152760860	152761120	0.001819056	-1.228266992	-1.043484356
chr3	152760860	152761120	0.001819056	-1.228266992	-1.043484356
chr19	39137880	39138760	0.001816547	-1.109609538	-0.891167108
chr20	20300800	20301340	-0.001814735	-1.025281198	-1.36077188
chr6	31324740	31325180	0.001814206	-1.29357914	-0.996095078
chr11	117817200	117818460	0.001812738	-1.252515343	-1.010349762
chr2	192329240	192329640	-0.001812133	-0.988166375	-1.245620225
chr15	74753060	74754080	0.001811613	-1.337152716	-1.107402573
chr6	12680120	12680600	-0.001811591	-1.012100779	-1.245467031
chr3	192875300	192875700	0.00181138	-1.445056923	-1.247174375
chr3	128399400	128400140	0.001811323	-1.371294175	-1.066471895
chr6	16070820	16071220	-0.001810653	-1.04535823	-1.380084089

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr19	13044100	13045000	0.00181024	-1.207618924	-1.04491129
chr7	2490820	2491660	0.001807441	-1.160102301	-0.91871006
chr1	155989960	155991340	0.001803773	-1.150866957	-0.877689454
chr3	160282020	160283700	0.001803417	-1.319931378	-1.034191162
chr7	55639260	55640720	0.00180304	-1.202641744	-0.928984511
chr6	83953360	83953800	-0.001801785	-1.019426318	-1.306365216
chr6	153150560	153151020	-0.001801748	-0.894950521	-1.263116453
chr4	84453600	84454520	-0.001799843	-0.997078548	-1.294739185
chr2	175613640	175613920	0.001799382	-1.282570363	-0.982044975
chr6	6108580	6109180	-0.001798899	-0.856776324	-1.100207942
chr5	2623160	2623680	0.001798234	-1.166078723	-1.032502533
chr7	121180400	121180900	0.001797611	-1.185286934	-1.048168773
chr3	151986280	151987880	0.001797108	-1.235795903	-0.987353124
chr18	7021660	7022020	-0.001795644	-1.033381611	-1.372516711
chr10	87625480	87625920	-0.001794808	-0.898171333	-1.129884428
chr19	3985000	3986140	0.001794431	-1.20318186	-0.957074834
chr7	54265700	54266180	-0.001792861	-0.996047914	-1.181918678
chr5	173045980	173046260	0.001792352	-1.289601161	-1.028839787
chr15	35212480	35212760	0.001791998	-1.149896496	-0.88061882
chr14	23235220	23236540	0.001790519	-1.316081091	-1.050051172
chr10	30959960	30960260	0.001789428	-1.141223925	-0.889959216
chr6	129577660	129578180	-0.001789244	-1.022929588	-1.296476801
chr12	110869660	110870040	-0.001786508	-0.974705003	-1.276579815
chr21	16162120	16162500	-0.00178376	-0.85005859	-1.098942835
chr5	145562080	145562560	0.001782785	-1.299008385	-1.023677488
chr6	26596660	26597600	0.001782647	-1.348347128	-1.182107409
chr6	123895820	123896200	-0.001782231	-0.964495978	-1.239501762
chr10	129651800	129653080	0.001781754	-1.262666794	-0.976993587
chr5	5705840	5706620	-0.001781534	-1.031677331	-1.35901961
chr20	30864980	30866060	0.001777041	-1.12957985	-0.76334108
chr1	237245620	237246080	-0.001775549	-0.876094016	-1.087291364
chr21	20231300	20231780	0.001773473	-1.128272441	-0.885918544
chr21	20231300	20231780	0.001773473	-1.128272441	-0.885918544
chr14	79653740	79654200	0.001772057	-1.392981175	-1.038848153
chr2	27649940	27650400	-0.001771784	-1.018856367	-1.285285496
chr12	78982340	78982940	0.001771383	-1.295624438	-1.114862765
chr4	84453500	84454640	-0.001770829	-0.994385148	-1.278142937
chr17	74117060	74118940	0.001770116	-1.201780317	-0.936350787
chr1	172663140	172663400	-0.001768812	-0.993792317	-1.232789091
chr1	172663140	172663400	-0.001768812	-0.993792317	-1.232789091
chr9	1104920	1105520	-0.001768092	-0.611578364	-1.023597246
chr7	19647860	19648820	0.001767783	-1.165707927	-0.897877046
chr21	46008500	46008720	-0.001766549	-0.730908746	-1.067209279
chr21	46008500	46008720	-0.001766549	-0.730908746	-1.067209279
chr2	167167720	167168060	-0.001765014	-1.009931771	-1.244409402
chr1	10532500	10532820	0.00176413	-1.256777033	-1.02024304
chr3	42829040	42829320	-0.001763178	-0.890703282	-1.173796372
chr5	150632160	150633280	-0.001762481	-0.880561696	-1.073022758
chr11	110518720	110519180	-0.00176193	-1.050632739	-1.315258747
chr3	149526060	149526340	0.001761617	-1.362245976	-1.132139347
chr6	7723280	7723580	0.001761529	-1.288711661	-0.950824528
chr11	70048340	70050300	0.001760506	-1.399675847	-1.117597544
chr6	16593820	16594560	-0.001760267	-0.945359005	-1.285479954
chr1	73435720	73436060	-0.001759591	-0.751495052	-1.133330527
chr13	77054320	77054580	0.001756602	-1.241454974	-1.047404335
chr13	42429220	42429780	-0.001756486	-1.050334505	-1.34474535
chr7	80847140	80847680	-0.001756106	-0.836598874	-1.152143238
chr2	5856360	5856740	-0.001751463	-0.83597468	-1.124499557
chr6	68151720	68152160	-0.001750467	-1.021728072	-1.259540327
chr11	60927840	60929680	0.00175006	-1.323171898	-1.108509806
chr6	151987660	151988100	0.001749569	-1.278237632	-1.00434993
chr11	65626840	65627160	0.001746697	-1.400438343	-1.165384487
chr1	6569360	6569660	0.001746608	-1.144538957	-0.864020538
chr1	244553000	244553520	0.001746061	-1.156244067	-1.010300338
chr8	19674320	19675800	0.001746	-1.259330763	-0.958927902
chr2	192430580	192431740	0.001745801	-1.241725258	-0.89011032
chr2	39643100	39643320	-0.001745113	-0.861266131	-1.10534045
chr6	40604280	40604940	-0.001744313	-0.879010153	-1.172329832
chr2	216973280	216974700	0.001743164	-1.326584866	-1.129055722
chr4	143303560	143304060	-0.001742047	-1.063460069	-1.344866457
chr6	100335120	100335480	-0.001741542	-1.048063232	-1.331089324
chr17	76919280	76919620	0.001741477	-1.111801004	-0.972363198

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr20	47804080	47805480	0.001738927	-1.326170129	-1.035640462
chr12	14762280	14762800	-0.001738903	-0.893288218	-1.211149445
chr21	27905300	27905760	-0.001738678	-0.643528798	-0.945033912
chr1	75126160	75126540	-0.001738135	-0.761425205	-1.051786736
chr6	33128800	33129960	0.001737721	-1.312484679	-0.987068498
chr16	68271380	68271860	0.001736829	-1.161591467	-0.820710301
chr15	59312100	59312660	-0.001735591	-0.762275717	-1.153328779
chr20	23618120	23619520	-0.001735261	-0.947641183	-1.099002751
chr21	28895480	28895940	-0.001734928	-0.781910668	-1.113819022
chr21	45557880	45558160	0.001734693	-1.124273086	-0.778764573
chr3	194338920	194339580	-0.001734085	-0.961465004	-1.312051536
chr19	6429140	6429340	-0.00173406	-0.858684978	-1.195171502
chr16	17849140	17849540	-0.001731474	-0.827805134	-1.125462834
chr8	20807100	20807580	-0.001729889	-1.090107369	-1.338023403
chr3	8051740	8052300	-0.001729854	-1.023701557	-1.287743187
chr16	85336660	85337480	0.00172983	-1.079964428	-0.798703969
chr21	43092520	43093560	0.001729761	-1.089626899	-0.68305534
chr21	39231640	39231960	-0.001729405	-0.819108796	-1.059766945
chr1	35703200	35703680	-0.00172916	-1.008184022	-1.279741506
chr2	55524240	55524560	-0.00172847	-0.882147997	-1.173705257
chr11	64878660	64878880	0.001727931	-1.191267554	-0.934874465
chr17	56190120	56191060	0.001727558	-1.165987886	-0.944658718
chr11	123984880	123985600	-0.001724882	-0.956087828	-1.204894368
chr4	70957640	70958120	-0.001724235	-1.048870702	-1.270490777
chr17	781400	782000	-0.001724154	-0.875705326	-1.055358856
chr1	35703260	35703640	-0.001723328	-0.988722861	-1.271963656
chr13	64549560	64549920	-0.001721016	-1.005887771	-1.229575737
chr13	64549520	64549960	-0.001721016	-1.005887771	-1.229575737
chr6	167061140	167061960	-0.001720665	-0.826858861	-0.954227694
chr5	81329440	81329980	0.001720664	-0.985776945	-1.301856776
chr5	14351860	14352940	0.001719992	-1.220917597	-0.945499494
chr10	129651980	129652880	0.001718821	-1.223771891	-0.958700177
chr3	86036600	86037040	-0.001717211	-1.026491844	-1.332356872
chr12	125347700	125349340	0.001716106	-1.348861442	-1.136789015
chr9	30752940	30753340	-0.001715743	-0.694047711	-1.025655201
chr2	77100400	77100800	-0.0017142	-0.854366259	-1.167591256
chr1	45262120	45262360	-0.001714185	-0.834196995	-1.050385574
chr2	229128160	229128500	-0.001713136	-0.916394002	-1.191976206
chr2	86041060	86041960	0.001711709	-1.134735434	-0.926637525
chr3	156310600	156311040	-0.001711465	-0.996472958	-1.37243759
chr6	3852080	3852500	-0.001710872	-1.031718856	-1.200633657
chr7	25019060	25020420	0.001709465	-1.132717218	-0.894046798
chr3	197519380	197519600	-0.001707827	-1.090936757	-1.380632354
chr17	26971520	26972460	0.001706283	-1.156063571	-0.867016715
chr12	69550840	69551140	0.001705857	-1.263667892	-1.011940371
chr12	7062980	7063300	0.001705247	-1.314488286	-1.017860338
chr13	62654600	62655100	-0.001705158	-1.126667646	-1.363631702
chr9	136022980	136023180	-0.001704601	-0.906866869	-1.02970209
chr11	96105560	96106160	-0.001703807	-1.063057146	-1.371390852
chr15	75660120	75661180	0.00170334	-1.138256196	-0.888217117
chr1	169304840	169305160	-0.001700785	-0.860621891	-1.132814291
chr2	37747060	37747460	0.001700254	-1.160451951	-0.993448778
chr19	58513600	58514940	0.001699424	-1.112306129	-0.879981171
chr4	52976620	52977060	-0.001697189	-0.904545709	-1.218341753
chr14	46973720	46974200	0.001695403	-1.246281736	-1.039818042
chr19	58089680	58090980	0.001694225	-1.089900508	-0.855404993
chr22	31503120	31504260	0.001693593	-1.075100448	-0.836750942
chr1	117117260	117117560	0.001693353	-1.361859533	-1.069390233
chr2	238581740	238582540	0.001692576	-1.233049783	-0.886686257
chr6	68151700	68152200	-0.001692412	-1.046872273	-1.297953681
chr3	11313800	11314300	0.001691393	-1.334284405	-1.09279344
chr17	58041760	58042560	0.001690054	-1.250898652	-1.072470864
chr22	31627180	31627480	0.001689614	-0.989139001	-0.759994327
chr2	1259400	1260040	-0.00168858	-1.009662749	-1.25065727
chr12	68725480	68727140	0.001685362	-1.369584237	-1.126726437
chr7	135723100	135723480	-0.001683674	-0.827197135	-1.119759947
chr19	1089280	1089540	0.0016819	-1.017523334	-0.781426098
chr17	2206160	2207460	0.001679437	-1.124100687	-0.847558428
chr5	31292700	31293200	-0.001678886	-1.025157917	-1.18164671
chr11	46388900	46389780	0.001677774	-1.235001314	-0.971950386
chr4	73395140	73395640	-0.001676882	-1.048203835	-1.345566123
chr12	89936760	89937020	0.001676621	-1.254084726	-1.011936134

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr13	57458980	57459480	-0.001676168	-0.982350314	-1.260000772
chr7	78843480	78844460	-0.00167616	-0.968020636	-1.233772483
chr10	50356720	50357140	-0.001676119	-1.016517169	-1.294223011
chr3	103290480	103290900	-0.001675934	-0.998726485	-1.294817608
chr3	188240420	188240740	-0.00167537	-1.047325458	-1.231163742
chr1	153930260	153931820	0.001675349	-1.212723567	-1.014229284
chr8	66274840	66275300	-0.001674739	-0.963460725	-1.12509728
chr15	67639960	67640420	-0.001674313	-0.820087292	-1.13517581
chr19	12035680	12036000	0.001673782	-1.272729988	-1.066418305
chr2	175311960	175312800	-0.001673324	-0.861221172	-1.11448268
chr18	51883720	51884880	0.001670837	-1.325131562	-1.149232103
chr7	157744760	157745300	0.00166978	-1.106542763	-0.735315622
chr17	70556080	70557000	0.001669283	-1.082245914	-0.885462031
chr14	105956340	105958320	-0.001668235	-0.985989602	-1.132923133
chr4	165676540	165676920	-0.001668143	-1.188994522	-1.360187215
chr14	27268640	27268920	-0.001668096	-0.914904525	-1.27905516
chr10	107431600	107432080	-0.001666883	-1.072688392	-1.268020118
chr1	247357660	247357980	-0.001666693	-0.92656584	-1.16821754
chr9	80509040	80509400	-0.00166487	-0.755518216	-1.061514599
chr1	68458620	68459180	-0.001662997	-0.886176957	-1.201023011
chr6	56410980	56411360	-0.001662218	-1.048235148	-1.239251792
chr12	49457760	49458020	0.001661632	-1.294610017	-1.049742962
chr12	49457760	49458020	0.001661632	-1.294610017	-1.049742962
chr3	7768060	7768560	-0.001661077	-1.053979809	-1.318814564
chr16	81756760	81757080	0.00166032	-1.211849375	-0.944712785
chr8	79794780	79795360	0.001659996	-1.261393801	-1.165220012
chr12	7063000	7063320	0.001659946	-1.316058138	-1.043993786
chr12	62586480	62586780	0.001659735	-1.143728478	-0.915827913
chr12	62586480	62586780	0.001659735	-1.143728478	-0.915827913
chr7	111616220	111616500	-0.001659653	-0.905834879	-1.198525099
chr4	148814440	148814940	-0.001659119	-0.969385202	-1.25234665
chr16	55744820	55745360	0.00165839	-1.115694033	-1.069202302
chr9	96755820	96756200	-0.001657859	-0.764365979	-1.080295636
chr7	148762880	148763220	0.001657589	-1.253063946	-1.035750432
chr8	121310580	121311080	-0.001657251	-1.015432383	-1.272619566
chr6	129521080	129521840	0.001655127	-1.192855995	-1.050191286
chr2	178299500	178299980	-0.001653879	-0.816526192	-1.093640663
chr13	87800200	87800580	-0.001653092	-0.995346712	-1.226844566
chr14	41362960	41363480	-0.001652097	-1.100282497	-1.3387505
chr22	41157080	41157600	-0.001651765	-0.755027366	-1.155486288
chr9	112170900	112171360	-0.001651169	-0.745388168	-1.05627437
chr15	52970340	52972260	0.001650084	-1.045400322	-0.756017521
chr2	169833460	169833800	-0.001649268	-0.909290425	-1.137861953
chr9	11725740	11726180	-0.001649267	-0.797630046	-1.086294568
chr2	181278900	181279240	-0.001649087	-0.935627904	-1.127640353
chr2	181278900	181279240	-0.001649087	-0.935627904	-1.127640353
chr3	79898780	79899360	-0.001647845	-0.891628702	-1.173954608
chr14	55737780	55738800	0.001647584	-1.31831064	-1.00446761
chr6	91788120	91788680	-0.001647183	-0.942568342	-1.256917769
chr6	153150560	153151040	-0.001646725	-0.880639547	-1.250556264
chr19	17530460	17531520	0.001646484	-1.131241001	-0.874950967
chr12	87949960	87950460	-0.001646237	-1.104869052	-1.35527986
chr1	226312920	226313180	0.001645053	-1.272567014	-1.026719809
chr2	38091320	38091780	-0.001644507	-0.897058668	-1.209059159
chr19	4606720	4607140	0.001644501	-1.020703983	-0.831550159
chr9	75491200	75491560	-0.001644003	-0.750291667	-1.07949311
chr5	67045380	67045820	-0.0016439	-0.951134152	-1.20744774
chr16	1524440	1525860	0.001643408	-1.085077662	-0.779353372
chr8	68813660	68814060	-0.001641931	-0.908575578	-1.22988585
chr10	130010200	130010520	0.00164136	-1.270469574	-0.967614448
chr5	145562100	145562560	0.001641217	-1.300470795	-1.045935722
chr20	37678440	37679340	0.001641169	-1.341991547	-1.106253475
chr12	105580180	105580720	-0.001641142	-0.970544913	-1.197268047
chr8	36456600	36457020	-0.00164048	-0.937672334	-1.199854976
chr19	13210220	13210540	0.001640113	-1.120635263	-0.938994426
chr18	63122300	63123160	-0.001639573	-0.924892376	-1.322228651
chr11	26223580	26224100	-0.001638632	-1.033593501	-1.337980725
chr6	156953440	156953960	-0.001638246	-0.888026954	-1.136664864
chr11	24650820	24651240	0.001637451	-1.054629382	-0.922398151
chr18	70788460	70788740	-0.001636764	-0.891043114	-1.214079035
chr2	85154180	85154440	0.001636639	-1.306900321	-1.030822707
chr19	40954380	40954660	-0.001635953	-0.759015349	-1.089422743

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr19	40954320	40954720	-0.001635953	-0.759015349	-1.089422743
chr21	19299220	19299680	-0.001635097	-0.786302515	-1.07127293
chr2	213256220	213256680	-0.001634179	-1.019662327	-1.361173295
chr4	68253440	68254000	-0.001633697	-1.057276455	-1.299291853
chr3	78685900	78686320	-0.00163339	-1.177863676	-1.425974533
chr19	10675980	10677320	0.001633184	-1.04863403	-0.842592423
chr13	26722620	26723000	-0.001632981	-1.088615134	-1.317713644
chr13	26722560	26723060	-0.001632981	-1.088615134	-1.317713644
chr6	10412500	10412900	0.00163292	-1.268422766	-1.004447909
chr7	150941460	150941700	0.001632136	-1.14802976	-0.957526521
chr1	152055020	152055440	-0.0016321	-0.858829572	-1.068072159
chr18	28118720	28119000	-0.001631578	-0.949426462	-1.142231884
chr6	71275800	71277380	0.001631572	-1.338425067	-1.050318539
chr2	202843440	202843860	-0.001630077	-0.915509456	-1.205495194
chr4	179446320	179446740	-0.001629866	-1.137753909	-1.32774326
chr4	179446280	179446780	-0.001629866	-1.137753909	-1.32774326
chr1	153721440	153722720	0.001629123	-1.211772311	-1.039691763
chr2	144077820	144078220	0.001628538	-1.129984855	-0.909092392
chr1	69737580	69737980	-0.001626908	-0.991285414	-1.241454647
chr1	69737520	69738040	-0.001626908	-0.991285414	-1.241454647
chr2	57779080	57779500	-0.001626601	-0.907732627	-1.261871584
chr1	249119700	249121340	0.001626517	-1.288936759	-1.05475076
chr11	26223640	26224060	-0.001626492	-0.996056329	-1.295634437
chr3	8051760	8052260	-0.001626301	-1.046708748	-1.260361129
chr1	18001800	18003080	0.001625628	-1.17531584	-0.824571829
chr1	18001760	18003120	0.001625628	-1.17531584	-0.824571829
chr5	90850220	90850700	-0.001625359	-0.927967008	-1.226042817
chr5	90850220	90850700	-0.001625359	-0.927967008	-1.226042817
chr15	73414160	73414720	-0.001623901	-0.782172392	-1.021552089
chr8	132693560	132694180	-0.001623893	-0.946084036	-1.200404221
chr1	169304840	169305180	-0.001623638	-0.827976292	-1.108414211
chr10	27171000	27171260	0.001623443	-1.209075078	-1.017127802
chr10	271710980	27171280	0.001623443	-1.209075078	-1.017127802
chr9	30841780	30842300	-0.001622919	-0.744552338	-1.041632524
chr5	9710780	9711300	-0.001622528	-1.057346192	-1.280181416
chr6	83679600	83679980	-0.001622244	-0.884279549	-1.120123507
chr5	20242560	20242920	-0.001621432	-0.935016972	-1.228392575
chr6	56799180	56799580	-0.001621303	-1.025875306	-1.233246639
chr17	1390640	1390940	0.001621143	-1.168140291	-0.969734768
chr19	54370600	54371200	0.001621077	-1.061703058	-0.883349758
chr11	92026440	92026980	-0.001620878	-1.012961281	-1.260178375
chr5	99901660	99902100	-0.001619393	-1.05604558	-1.300252962
chr4	150264040	150264500	-0.001618448	-1.128667506	-1.346126544
chr4	150264020	150264520	-0.001618448	-1.128667506	-1.346126544
chr10	63780560	63781060	-0.001617841	-0.84208815	-1.125652283
chr2	224869580	224869980	-0.001617308	-1.076375934	-1.374404261
chr6	66169660	66170140	-0.00161694	-1.064454363	-1.25300256
chr17	75731660	75732140	0.001616451	-0.968008964	-0.756599012
chr8	1683660	1683940	0.001615473	-1.255054396	-1.01912457
chr2	70313760	70314980	0.001614536	-1.292140119	-1.114075244
chr12	133356280	133356980	0.001614053	-1.17549124	-0.908154156
chr10	126096660	126097120	-0.001613715	-0.956738249	-1.215107737
chr6	78744220	78744520	-0.001613152	-0.801707208	-1.077826047
chr15	40615600	40617080	0.001613065	-1.121546454	-0.855194144
chr15	40615560	40617120	0.001613065	-1.121546454	-0.855194144
chr15	53280240	53280940	0.001612461	-0.99668246	-0.918498723
chr5	103240760	103241220	-0.001611548	-0.844886114	-1.010625646
chr1	28969160	28969920	0.001610667	-1.141029428	-0.916120346
chr4	106199180	106199500	-0.001610408	-0.950294364	-1.16387358
chr13	77067040	77067440	-0.001610261	-1.11220931	-1.357563354
chr14	77338880	77339760	0.001610203	-1.370092449	-1.041847539
chr1	194181600	194182080	-0.001609339	-0.971434624	-1.216478939
chr11	7166320	7166660	-0.001607706	-0.917151216	-1.235231153
chr3	37901520	37902560	0.001607693	-1.359991245	-1.094561792
chr10	95545320	95546380	0.001606561	-1.38669291	-1.217112497
chr19	10206380	10207320	0.001606264	-1.178189621	-0.978580908
chr13	100994060	100994440	-0.001605455	-0.92487411	-1.193256482
chr2	159289360	159289960	0.001605021	-0.958218445	-0.803710037
chr5	162132200	162132680	-0.001604172	-0.960612409	-1.235544866
chr18	44593080	44593460	-0.001603385	-1.060816684	-1.2123037
chr7	53760900	53761380	-0.001602508	-1.003954141	-1.249764772
chr9	132222460	132223000	0.001602438	-1.187706327	-0.965072321

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr4	1713540	1715000	0.001601685	-1.354817925	-1.023663052
chr3	158445580	158445860	0.001601371	-1.372314433	-1.080882552
chr7	28776920	28777440	-0.0016012	-0.939330263	-1.220214255
chr4	74781140	74781580	-0.0016011	-0.940901781	-1.18763956
chr6	102473780	102474260	-0.001601006	-0.875018012	-1.088294948
chr10	14919800	14921480	0.001600893	-1.222248692	-0.996004968
chr11	60928260	60929340	0.001600241	-1.284231717	-1.074888768
chr16	67562080	67563200	0.001599976	-1.158540618	-0.898149352
chr19	12750960	12751280	0.001597994	-1.1387386	-0.961839117
chr15	46957840	46958380	-0.00159619	-0.920888826	-1.284558745
chr18	51883700	51884880	0.001595959	-1.325131562	-1.149077155
chr7	38145520	38145820	0.001595938	-1.156343129	-0.944351043
chr13	64232340	64232900	-0.001595071	-1.001909649	-1.252382471
chr15	90614540	90614800	0.001594572	-1.154808842	-0.8396283
chr2	60837200	60837660	0.001593688	-1.182460134	-1.00131585
chr15	66564120	66564600	-0.001592848	-0.755312829	-1.040601274
chr8	60417900	60418500	-0.001592124	-1.13762682	-1.398494557
chr8	60417900	60418500	-0.001592124	-1.13762682	-1.398494557
chr2	5856300	5856780	-0.001590526	-0.894171251	-1.145369253
chr1	1475120	1476160	0.001590243	-1.111949016	-0.9240611792
chr3	72094800	72095120	-0.001590165	-1.029451055	-1.295134721
chr11	62438940	62439260	0.001588103	-1.337514775	-1.005948152
chr16	82164020	82164860	0.001587796	-1.100356983	-0.94937981
chr7	150780260	150780780	0.001587795	-1.222003542	-0.954291242
chr7	150780280	150780760	0.001587795	-1.222003542	-0.954291242
chr1	67966140	67966460	0.001587162	-1.164197394	-0.844159857
chr3	126001120	126001500	-0.001586772	-0.964061481	-1.2341045
chr17	13272100	13272660	-0.001586627	-0.829086888	-1.195485854
chr16	89652120	89652700	0.001585959	-1.249306915	-0.972431702
chr10	119289420	119289820	-0.001585779	-0.865470472	-1.049650509
chr20	8497120	8497580	-0.00158547	-1.022481735	-1.242417957
chr20	54139380	54139880	0.001585161	-1.205135954	-1.062884522
chr20	12817100	12817480	-0.00158481	-0.989711008	-1.203432946
chr5	66748640	66749060	-0.001584096	-0.980846966	-1.196380008
chr17	56409820	56410080	0.001583996	-1.1494443658	-0.913326168
chr10	96390860	96391220	-0.00158368	-0.920480795	-1.236998778
chr22	37882340	37882620	0.001583673	-1.143144075	-0.85530824
chr19	10676020	10677060	0.001583294	-1.0301869	-0.78811203
chr3	175387940	175388620	-0.001581009	-0.853371954	-1.269444788
chr10	70286980	70287500	0.001580904	-1.237173833	-0.963584649
chr1	1274400	1274680	0.001580639	-1.094449154	-0.884375026
chr1	1274420	1274660	0.001580639	-1.094449154	-0.884375026
chr9	82358240	82358800	-0.001579271	-0.922655104	-1.216113246
chr8	78755580	78756000	-0.001578983	-1.101261792	-1.398378597
chr18	45893580	45893900	-0.001578604	-0.971920622	-1.162311375
chr10	88136540	88137780	0.001577935	-1.278202397	-0.980068184
chr5	90896900	90897360	-0.00157697	-0.923720428	-1.206023403
chr5	90896880	90897380	-0.00157697	-0.923720428	-1.206023403
chr7	44019280	44019260	0.001575115	-1.125241774	-0.80826051
chr5	176899760	176901160	0.001574524	-1.195434044	-0.964835491
chr3	86082700	86083180	0.001574314	-1.263062383	-1.093777395
chr3	86082640	86083240	0.001574314	-1.263062383	-1.093777395
chr9	104876000	104876740	-0.001574139	-0.796786242	-1.072749248
chr4	160482060	160482380	-0.001573523	-0.976932615	-1.211043446
chr4	111405800	111406040	-0.001573128	-0.971989156	-1.239298098
chr4	111405800	111406040	-0.001573128	-0.971989156	-1.239298098
chr7	64411680	64411940	0.001571026	-1.198219805	-0.9534773
chr17	65990500	65990740	-0.001569725	-0.986277328	-1.185906006
chr7	65990420	65990820	-0.001569725	-0.986277328	-1.185906006
chr5	21183280	21183680	-0.001569423	-0.939396931	-1.1918402
chr12	82041500	82041780	-0.001568618	-1.050086288	-1.328603913
chr7	52246600	52247140	-0.001567939	-0.86628472	-1.264828649
chr7	52246560	52247180	-0.001567939	-0.86628472	-1.264828649
chr10	14919740	14921560	0.001567503	-1.292713977	-1.060609026
chr12	57030520	57030780	0.001567322	-1.271993089	-1.095855567
chr3	88207660	88208300	-0.001566885	-1.068446972	-1.318221192
chr18	28226480	28227800	-0.001566777	-1.027671404	-1.372043853
chr3	26732320	26732840	-0.001566648	-1.026088133	-1.273086704
chr19	13961160	13961600	0.001565855	-1.141230052	-0.927119677
chr10	57301780	57302340	0.00156567	-1.133129027	-0.997685885
chr22	39925260	39925540	0.001565308	-1.130737642	-0.911547555
chr22	39924960	39925840	0.001565308	-1.130737642	-0.911547555

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr10	57109760	57110260	-0.001565168	-0.936651252	-1.211837666
chr12	84857160	84857600	-0.001564681	-1.039199465	-1.252789124
chr11	64512180	64513180	0.001564515	-1.129419649	-0.997515303
chr1	201528820	201529120	0.001564246	-1.226469072	-1.024641927
chr22	49770400	49770840	-0.001563803	-0.896685442	-1.150092456
chr21	19605040	19605500	-0.001563769	-0.875724356	-1.102331571
chr1	45262120	45262320	-0.00156361	-0.946455576	-1.1801493
chr19	42724180	42724560	0.001562713	-1.157981781	-0.911986881
chr19	42724180	42724560	0.001562713	-1.157981781	-0.911986881
chr21	18086360	18086820	-0.001560396	-0.795669945	-1.044214393
chr19	17530520	17531440	0.001560289	-1.148153139	-0.891563581
chr1	80805020	80805460	0.001559374	-1.069272978	-0.939809899
chr15	59821120	59821420	0.001558978	-1.185907415	-0.920596722
chr19	7694040	7694800	0.001558631	-1.03853981	-0.854724275
chr14	24603100	24603380	-0.001558518	-0.902027437	-1.137827085
chr7	66192540	66192860	0.001558416	-1.114796727	-0.903201533
chr7	66192540	66192860	0.001558416	-1.114796727	-0.903201533
chr3	195586220	195586500	0.00155795	-1.326685732	-1.028668869
chr3	88710340	88710780	-0.001557861	-0.969055041	-1.23695541
chr12	97221740	97221940	-0.001557575	-1.016168676	-1.282459858
chr4	52795460	52795940	-0.00155753	-0.925454969	-1.201482623
chr4	52795420	52795980	-0.00155753	-0.925454969	-1.201482623
chr21	17592900	17593380	-0.001557517	-0.847361868	-1.103072806
chr2	120516680	120518080	0.00155652	-1.230813383	-1.01548829
chr5	5778200	5778820	-0.001556414	-0.946680774	-1.310027378
chr5	84968640	84969760	-0.001554712	-0.903071743	-1.23915503
chr10	47664260	47665040	0.001554095	-1.213820849	-0.852073472
chr10	47664240	47665060	0.001554095	-1.213820849	-0.852073472
chr3	120343260	120343740	-0.001553392	-0.941425091	-1.14060262
chr19	51250960	51251440	0.001552475	-1.075952503	-0.99250022
chr16	813640	813980	0.001551788	-1.113202823	-0.957864884
chr3	174573380	174573920	0.001551281	-1.174127584	-0.994205333
chr19	2307740	2308720	0.001551048	-1.197329904	-0.994665843
chr5	45203440	45204460	-0.00155074	-0.922563322	-1.188975948
chr14	64413080	64413620	-0.001550262	-0.893751825	-1.199203436
chr11	111883820	111884300	-0.001549448	-1.000205789	-1.116960297
chr3	14197760	141978260	-0.001549383	-1.163726381	-1.336305758
chr9	121152480	121153160	-0.001549272	-0.769334793	-1.075706504
chr6	29052020	29052560	-0.001549006	-1.063245645	-1.2934236
chr6	52149140	52149980	0.001548278	-1.220131354	-0.970037734
chr1	11865340	11866680	-0.001548163	-0.9307811	-1.052281109
chr6	26596040	26598260	0.001547451	-1.361450155	-1.207373165
chr16	31438720	31439740	0.001547119	-1.222613119	-1.002707737
chr18	41210920	41211520	-0.001546124	-1.002567351	-1.296333237
chr10	30960000	30960260	0.001545912	-1.256186178	-0.99648725
chr10	46079420	46079780	-0.001545424	-0.845550128	-1.160475667
chr3	48442320	48442600	0.001544454	-1.325717782	-0.943920032
chr9	33165980	33166220	0.001544389	-0.926745294	-0.617754809
chr14	44908660	44909200	-0.001544007	-0.990389207	-1.195928563
chr5	159835560	159836100	-0.001543652	-0.995621206	-1.319329846
chr5	26811320	26811860	-0.001543176	-0.91651889	-1.171077986
chr3	78685840	78686360	-0.001542321	-1.176705658	-1.4193861
chr1	29062980	29064000	0.001541164	-1.058867864	-0.9009758587
chr19	37115760	37116220	-0.001540786	-0.965068329	-1.164887391
chr4	187572040	187572420	-0.001540274	-0.836345637	-1.148070929
chr19	13212500	13212820	0.001540121	-1.104143207	-0.959841416
chr19	32237880	32238960	0.001540028	-1.069893288	-0.969319325
chr5	51806920	51807360	-0.001539954	-0.973809344	-1.288346269
chr3	115526940	115527220	0.001539716	-1.221996654	-1.008828902
chr3	115526940	115527220	0.001539716	-1.221996654	-1.008828902
chr2	109228160	109228760	-0.001539691	-0.96379041	-1.156842311
chr2	109228160	109228720	-0.00153968	-1.016516158	-1.231900377
chr13	86190840	86191660	-0.001539207	-0.943260775	-1.269499956
chr17	56076600	56077520	0.001538641	-1.136854608	-0.971730166
chr8	113422600	113423120	-0.001538028	-1.071580226	-1.331870373
chr16	23568200	23569520	0.001537183	-1.12220963	-0.994556664
chr3	22320780	22321260	-0.001534906	-0.790819497	-1.13146817
chr7	129073660	129074860	0.001534832	-1.14038255	-0.886826813
chr11	60666860	60667140	0.001533479	-1.33976372	-1.075166854
chr17	77070580	77071620	0.001533398	-1.079890843	-0.897720019
chr17	29248780	29249640	0.001532524	-1.17513259	-0.80061273
chr1	72364280	72364960	0.001532422	-1.241236205	-1.099085484

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr8	116333480	116333980	-0.001532215	-0.9525287	-1.194714748
chr13	97868980	97869580	-0.001532132	-1.056090706	-1.366018339
chr1	166161460	166161920	-0.001531356	-0.908912522	-1.172151698
chr8	16546560	16547040	0.001531106	-1.299927299	-1.019347751
chr17	38115240	38115540	0.001531054	-1.271909935	-0.988397151
chr5	130031880	130032280	-0.001531042	-1.078325572	-1.354242678
chr3	16579620	16579920	-0.001530068	-1.052459028	-1.352737068
chr20	37100660	37102400	0.001529447	-1.214256614	-1.025042724
chr12	83425880	83426240	-0.001529354	-0.935940265	-1.139002106
chr12	22763700	22764220	0.001529008	-1.276045813	-1.188003895
chr13	87800120	87800620	-0.001528977	-0.860877255	-1.090679186
chr18	31376700	31377200	-0.001528703	-1.012348927	-1.315266506
chr18	1504520	1504940	-0.001528701	-1.084187038	-1.325312888
chr18	1504480	1504980	-0.001528701	-1.084187038	-1.325312888
chr4	115953660	115954960	-0.001528437	-0.843640427	-1.061573845
chr11	36531140	36532700	0.001528249	-1.242547783	-1.010095124
chr15	44483920	44484320	-0.001527466	-0.838333694	-1.131542055
chr15	44483880	44484360	-0.001527466	-0.838333694	-1.131542055
chr2	232574940	232575280	0.001527448	-1.282954858	-1.109127243
chr8	55078780	55079040	0.001527201	-1.177494707	-0.980667709
chr1	11865340	11866600	-0.001526077	-0.929024546	-1.024324745
chr3	22571960	22572600	-0.001525951	-1.000140393	-1.327303122
chr16	23264040	23264420	-0.001525847	-0.900010023	-1.154476132
chr20	57580580	57580900	0.001525594	-1.230367164	-0.967910805
chr16	30661580	30662420	0.001524714	-1.167269147	-0.970979016
chr1	163725720	163726080	-0.001524591	-0.963571632	-1.241980873
chr17	70631760	70632200	-0.001524262	-0.875562446	-1.160124962
chr17	70631720	70632240	-0.001524262	-0.875562446	-1.160124962
chr12	75728120	75728420	0.001523799	-1.31206647	-1.054496399
chr19	54665940	54666340	0.001523018	-1.207765948	-1.002621694
chr16	4741920	4742220	0.001521989	-1.053298183	-0.834987204
chr1	119272320	119272900	-0.001521921	-1.001448499	-1.303680549
chr9	126981020	126981280	0.001521786	-1.013256128	-0.781131622
chr9	126981020	126981280	0.001521786	-1.013256128	-0.781131622
chr15	64930000	64930420	-0.001521263	-0.774336255	-1.098813107
chr8	50801120	50801640	-0.001520657	-1.093995803	-1.388519407
chr1	242607740	242608300	-0.001520219	-0.898893934	-1.182689877
chr4	158751440	158751700	0.001519781	-1.29238797	-1.150783063
chr4	158751440	158751700	0.001519781	-1.29238797	-1.150783063
chr5	117875120	117876260	-0.001519276	-0.972600766	-1.191123959
chr2	241505200	241506480	0.001519178	-1.10326174	-0.967896596
chr7	125159000	125159940	-0.001519114	-1.134017536	-1.37321394
chr7	143077280	143079060	0.001518856	-1.251291979	-1.073211217
chr6	69236800	69237080	-0.001518257	-0.941927078	-1.159546164
chr16	2041700	2043200	0.001517923	-1.261841296	-1.070655826
chr11	33278480	33280160	0.001517147	-1.24358559	-0.984890349
chr9	75491200	75491640	-0.001517139	-0.692568637	-0.960417528
chr22	24551060	24553220	0.001517032	-0.987780092	-0.80570395
chr20	20300740	20301500	-0.001516684	-1.037561598	-1.322200086
chr15	65590100	65590360	0.001516258	-1.128429446	-0.915959659
chr2	120516560	120518420	0.001515343	-1.164304273	-0.89815653
chr18	24941620	24942260	-0.001515212	-1.030682732	-1.16911929
chr21	43933620	43934700	0.001515009	-1.074990128	-0.784008813
chr6	75039880	75040400	-0.001514259	-0.994029795	-1.304360336
chr5	159835640	159836060	-0.001514206	-1.04740576	-1.341884151
chr17	27944980	27945340	0.001513651	-1.219175939	-0.980711226
chr6	132203540	132203960	0.001513398	-1.256635803	-1.140306153
chr7	29448420	29448700	0.001513293	-1.280428399	-1.021687562
chr6	26031160	26031600	-0.001512746	-1.021233603	-1.281434227
chr1	72153760	72154240	-0.001512361	-0.960992306	-1.201482563
chr10	66313440	66313820	-0.001511997	-0.992707592	-1.273813396
chr7	88591780	88592300	0.001511443	-1.135335282	-1.013655449
chr15	41694540	41694880	0.001511322	-1.2855103	-1.094417252
chr15	41694540	41694880	0.001511322	-1.2855103	-1.094417252
chr5	27636120	27636500	0.001511186	-1.264368707	-1.124118825
chr5	27636120	27636500	0.001511186	-1.264368707	-1.124118825
chr2	239228500	239229800	-0.001511132	-1.040983793	-1.153680891
chr16	68344380	68345520	0.00150991	-1.109176455	-0.896747692
chr1	24155580	24156020	-0.001509774	-0.92991535	-1.191102116
chr6	41316620	41317180	-0.001509475	-0.882883441	-1.209327928
chr21	47555200	47556000	-0.001508663	-0.769546043	-0.867540165
chr6	139308280	139309960	0.001508503	-1.268036539	-0.960574011

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr16	89574280	89574940	0.001507958	-1.145164717	-0.953243983
chr11	128564740	128565060	0.001507675	-1.151441955	-0.853983207
chr19	1146560	1147000	0.001507194	-1.118656083	-0.880862778
chr15	92395940	92397700	0.001506916	-1.258232023	-1.020573288
chr11	31987560	31988000	-0.001506566	-0.943449321	-1.311376206
chr8	145023280	145023540	0.001506266	-1.153244889	-0.923213947
chr17	43024540	43025880	0.001505815	-1.208900206	-1.037386423
chr2	205916940	205917360	-0.001505333	-1.167450951	-1.302265037
chr19	1855320	1855680	0.001504755	-1.03005901	-0.888606973
chr8	121310640	121311040	-0.001504388	-1.07742818	-1.281104267
chr16	2551240	2551520	0.001504033	-1.187391318	-0.893436804
chr2	162623380	162623980	-0.001504007	-1.07365009	-1.335101856
chr8	135724540	135725960	0.001503225	-1.27893126	-1.132817148
chr2	127807480	127808360	0.001503165	-1.18760904	-0.925364834
chr2	46682960	46683460	-0.001502807	-0.910116094	-1.164250162
chr11	12303140	12304020	0.001502573	-1.308463657	-1.085984096
chr7	81774400	81775240	-0.001502357	-0.929904735	-1.195951571
chr7	81774360	81775280	-0.001502357	-0.929904735	-1.195951571
chr19	14428900	14429340	-0.001501718	-0.92749128	-1.158924235
chr7	129697060	129697440	-0.0015012	-1.097873849	-1.335046655
chr8	109905540	109905940	-0.001500894	-0.965796876	-1.202000538
chr12	1702960	1704500	-0.001500792	-1.117942899	-1.229586746
chr1	156115820	156116080	0.001500676	-1.167615656	-0.883774245
chr2	198227000	198227600	0.001500606	-1.255235725	-1.179416973
chr14	85558700	85559360	-0.001500606	-0.936544958	-1.172460593
chr14	48009540	48010000	0.001500076	-1.126728693	-0.921083094
chr6	75039940	75040360	-0.00150006	-1.009438658	-1.279184566
chr1	36240340	36240600	0.001499808	-1.242686912	-0.967155275
chr10	95545360	95546380	0.001499788	-1.38669291	-1.222485934
chr17	5319440	5319680	0.00149935	-0.9357823	-0.791207127
chr5	25257840	25258360	-0.00149873	-0.866752019	-1.180493986
chr22	45831600	45831900	0.001497999	-1.063202178	-0.886143711
chr11	40782200	40782660	-0.001497929	-0.989516488	-1.169373239
chr1	115052800	115054680	0.001497683	-1.261156534	-1.024133395
chr2	172260340	172260820	-0.001496702	-0.991953703	-1.217862581
chr18	71151620	71152080	-0.001496373	-1.176439797	-1.365719861
chr17	7566360	7566620	-0.001494871	-0.669385954	-0.954574768
chr18	19903480	19904080	-0.001494779	-0.995059167	-1.319525312
chr6	154132220	154132680	-0.001494773	-1.102690991	-1.353735252
chr17	33390580	33390960	0.001494018	-1.152518702	-0.868324805
chr4	187997460	187997960	-0.001493842	-1.066179951	-1.268682536
chr19	33382860	33383200	0.001493281	-1.076583589	-0.985068107
chr19	33382860	33383200	0.001493281	-1.076583589	-0.985068107
chr3	132135600	132136960	0.001492677	-1.223227574	-1.016514706
chr2	173817760	173818340	-0.001492121	-0.959513867	-1.283204553
chr2	173817760	173818340	-0.001492121	-0.959513867	-1.283204553
chr1	192777600	192778460	0.001491751	-1.284605232	-1.048939135
chr17	7253500	7253920	0.001491127	-1.010430569	-0.86491446
chr6	48858000	48858460	-0.001490789	-0.925397227	-1.258514175
chr6	48857980	48858480	-0.001490789	-0.925397227	-1.258514175
chr15	50971500	50971960	-0.001490508	-1.016808968	-1.232502259
chr1	5871200	5871660	-0.001490334	-1.033131356	-1.177239554
chr11	7166260	7166700	-0.00149022	-0.954867457	-1.240492526
chr2	173486200	173486500	-0.001490046	-0.863051591	-1.201048699
chr2	173486200	173486500	-0.001490046	-0.863051591	-1.201048699
chr16	25026060	25027360	0.001489233	-1.204091409	-0.990719479
chr3	182697320	182699140	0.001488411	-1.233196703	-0.989689651
chr3	141977800	141978200	-0.001488118	-1.172173076	-1.349013807
chr21	29028000	29028600	-0.001487698	-0.894218737	-1.151688078
chr12	57753600	57753900	-0.001487521	-1.031662497	-1.191449797
chr8	65266100	65266600	-0.001487014	-1.059620384	-1.335748212
chr10	70287020	70287480	0.001486673	-1.256816394	-1.001330288
chr15	101457900	101458800	0.001486592	-1.154274754	-0.958792453
chr4	166247760	166249300	0.001486575	-1.377867498	-1.174409938
chr4	31331860	31332300	-0.001486334	-1.034436774	-1.222650299
chr17	61776760	61777240	0.001485967	-1.239618482	-0.97687258
chr10	33692380	33692800	0.001485933	-1.0061804	-1.155218718
chr10	33692380	33692800	-0.001485933	-1.0061804	-1.155218718
chr18	41940120	41940480	-0.001485899	-1.002658796	-1.248161593
chr2	203499360	203500900	0.001484981	-1.169217672	-0.9601797
chr20	42272060	42273140	0.00148485	-1.332411501	-1.172827976
chr20	42272060	42273140	0.00148485	-1.332411501	-1.172827976

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr12	123850300	123850540	0.001484722	-1.200657204	-0.975864961
chr14	102185000	102185740	-0.001483931	-0.952971462	-1.102026296
chr14	102184980	102185760	-0.001483931	-0.952971462	-1.102026296
chr9	27887800	27888260	0.0014838	-0.938687255	-0.858457396
chr10	86261420	86261840	-0.001483513	-0.890954548	-1.076236071
chr20	25370560	25371820	0.001482714	-1.372598886	-1.134417862
chr17	7738180	7739140	0.001482531	-1.132365921	-0.946937515
chr8	33443680	33444140	-0.001482367	-1.044129478	-1.281632377
chr6	9787580	9788160	0.001482328	-1.143932826	-1.028654826
chr6	9787600	9788140	0.001482328	-1.143932826	-1.028654826
chr2	124159760	124160120	-0.00148196	-1.04461634	-1.201964065
chr11	65192740	65192940	0.001481843	-1.232327613	-1.019497428
chr10	57301800	57302340	0.001481522	-1.114454218	-1.005654604
chr5	148085040	148085240	-0.001481377	-0.894351035	-1.186616515
chr5	148085040	148085240	-0.001481377	-0.894351035	-1.186616515
chr16	76754340	76754640	-0.001480798	-0.676387671	-1.042152789
chr16	76754340	76754640	-0.001480798	-0.676387671	-1.042152789
chr17	76347200	76347580	0.001480392	-1.079669266	-0.88005833
chr11	6703800	6705280	0.001480169	-1.152490979	-0.970457783
chr9	100916480	100916800	-0.001479956	-0.72768643	-1.049632787
chr19	41814460	41814720	0.001479692	-1.18742561	-0.999889369
chr1	215202660	215203180	0.00147921	-1.160309782	-1.10450622
chr18	48657480	48657960	-0.001478619	-1.008979256	-1.217979855
chr4	158667240	158667820	-0.001478519	-1.084838791	-1.392285559
chr17	7342600	7342880	0.001477739	-0.986259785	-0.775387464
chr3	118653920	118654420	-0.001476673	-0.959592504	-1.179910323
chr17	67565220	67565500	0.001476447	-1.24505474	-1.077809833
chr7	53436740	53437380	-0.001475994	-0.722967328	-0.997844986
chr3	162566540	162566740	0.001475749	-1.425553627	-1.222765299
chr14	72070580	72070880	-0.001475431	-0.921370385	-1.148453247
chr14	72070580	72070880	-0.001475431	-0.921370385	-1.148453247
chr11	6494220	6495500	0.001475131	-1.203951587	-0.918679478
chr1	109942040	109942320	0.001474932	-1.194986089	-1.0100893
chr1	109942040	109942320	0.001474932	-1.194986089	-1.0100893
chr16	20991340	20991760	-0.001474898	-0.917156678	-1.245456233
chr14	72849720	72850100	0.001474562	-1.184742975	-1.028977429
chr5	58912520	58912980	-0.001474497	-1.012138025	-1.25547214
chr5	58912500	58913000	-0.001474497	-1.012138025	-1.25547214
chr6	90077600	90078460	0.001474288	-1.132591839	-0.949336228
chr3	107436840	107437400	-0.001473968	-1.019915243	-1.215837885
chr13	29232460	29234020	0.0014739	-1.326175133	-1.03053414
chr17	63096460	63097380	0.001473891	-1.101566576	-0.910762776
chr3	197236540	197237800	0.001473775	-1.301610206	-1.082307979
chr11	106882080	106882500	-0.001473736	-0.921072069	-1.25915629
chr12	56440900	56441300	0.001473681	-1.15746157	-0.965505448
chr11	63974980	63975220	0.001473632	-1.130377952	-0.887251879
chr17	28258420	28258680	0.001473452	-1.051189776	-1.009864147
chr9	92221620	92221980	-0.001472816	-0.757670747	-0.862411352
chr7	125730880	125731500	-0.00147264	-0.972561623	-1.270415794
chr20	30101900	30102400	0.001471765	-1.329491898	-1.114019872
chr6	16070760	16071220	-0.00147156	-0.977489715	-1.29740558
chr17	8648940	8649740	0.001471187	-1.122659106	-0.934493378
chr7	8648940	8649740	0.001471187	-1.122659106	-0.934493378
chr2	123477020	123477400	-0.001470845	-1.073406361	-1.315550387
chr3	29511240	29511760	0.001470465	-1.198260694	-1.118572894
chr3	87399720	87400220	0.001470286	-1.305266741	-1.071381226
chr9	76289320	76290320	-0.001470157	-0.897014528	-1.228504179
chr13	45012180	45012400	0.001470064	-1.212193837	-1.024611683
chr13	45012180	45012400	0.001470064	-1.212193837	-1.024611683
chr3	61752120	61752520	-0.00146977	-0.930757105	-1.188405511
chr19	52097040	52098260	0.001469677	-1.155065159	-0.922807632
chr21	17736760	17737260	-0.001469578	-0.712763283	-0.969308837
chr19	796640	798380	0.001469426	-1.192750729	-1.045742068
chr14	77339180	77339440	0.001469188	-1.352863634	-1.029725588
chr20	6787380	6787880	0.001468892	-1.183067642	-1.099765336
chr13	50639180	50639400	-0.001468816	-1.0772544	-1.267959581
chr13	50639180	50639400	-0.001468816	-1.0772544	-1.267959581
chr2	150633680	150634260	-0.001468461	-0.893717583	-1.130230342
chr4	109025340	109025840	-0.001468401	-0.895341052	-1.189149135
chr11	2216180	2216440	-0.00146803	-0.853918539	-0.983133651
chr8	103643720	103644540	-0.001468017	-1.077520799	-1.384889414
chr12	126330740	126331220	-0.001467969	-0.992731775	-1.195159116

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr2	220142440	220142700	0.001467941	-1.360907556	-1.033373989
chr2	220142440	220142700	0.001467941	-1.360907556	-1.033373989
chr11	567800	569280	-0.001466893	-1.045502775	-1.114934749
chr15	40613140	40613420	0.001466508	-1.231494384	-0.983414554
chr8	20807140	20807560	-0.001466371	-1.062630901	-1.301326813
chr8	84332600	84333080	-0.001466359	-1.05389805	-1.192870493
chr1	167503100	167503380	0.001466238	-1.23556292	-0.99664247
chr13	64647960	64648540	-0.001465974	-1.117138768	-1.348889828
chr19	54061940	54063380	0.001465019	-0.971926567	-0.792135223
chr19	2307800	2308720	0.001464643	-1.134280639	-0.97119594
chr13	54228040	54228520	-0.001464474	-1.067628614	-1.328747895
chr7	3868400	3868680	0.001463555	-1.114802789	-0.910186534
chr7	71570580	71571020	-0.001463458	-0.887765707	-1.114819309
chr7	71570560	71571040	-0.001463458	-0.887765707	-1.114819309
chr3	81746900	81747500	-0.001463243	-0.903104719	-1.173024915
chr13	104296060	104296320	-0.001462913	-0.801437034	-0.944285099
chr20	41396140	41396620	-0.001462798	-0.956024097	-1.256907709
chr10	125754160	125754440	0.001462783	-1.330803748	-1.060405745
chr5	108024880	108025340	-0.001462705	-0.971930952	-1.192975425
chr14	94468180	94468440	0.001461127	-1.211298598	-0.991168138
chr10	127511240	127512240	0.001461032	-1.198921449	-0.99374395
chr8	68402560	68402840	0.001460833	-1.184641244	-1.022193621
chr4	48780800	48782760	0.00146039	-1.280733137	-1.060899854
chr10	24617760	24618380	-0.001460073	-0.95491963	-1.320825755
chr14	46954720	46955180	-0.001459978	-0.987432147	-1.205233246
chr9	22227940	22228480	-0.001459633	-0.922231497	-1.124752463
chr6	127850260	127850920	-0.001459511	-0.988497756	-1.329549767
chr10	26624040	26624320	0.001459425	-1.191651933	-0.975722582
chr7	140291540	140291920	-0.001458664	-1.119363194	-1.312999525
chr19	45946680	45947840	0.001458249	-1.006881991	-0.843013892
chr19	45946660	45947860	0.001458249	-1.006881991	-0.843013892
chr2	181318140	181318520	-0.001457287	-0.940451536	-1.187305649
chr2	181318100	181318560	-0.001457287	-0.940451536	-1.187305649
chr7	128544760	128545020	0.001456791	-1.074098476	-0.81108403
chr7	128544760	128545020	0.001456791	-1.074098476	-0.81108403
chr22	46402260	46402520	0.001456653	-1.178284895	-0.995456444
chr21	46312740	46313000	0.001456395	-1.149343406	-0.866281386
chr19	10526900	10528120	0.001456097	-1.111876888	-0.893748837
chr4	106835440	106835660	-0.001456046	-1.091819655	-1.318528486
chr5	23418200	23418660	-0.001455801	-0.94542242	-1.24605923
chr11	92204880	92205360	-0.001454996	-0.991982825	-1.239841643
chr3	197281500	197281980	0.001454681	-1.290936593	-1.092912012
chr14	73490040	73490320	-0.001454348	-0.911932645	-1.199930155
chr3	192875500	192876380	0.001454372	-1.408587272	-1.250941495
chr4	16900080	16900700	-0.001453541	-1.071163773	-1.266419273
chr1	28198880	28199240	0.001453373	-1.216789058	-1.065658013
chr13	88557600	88558080	0.001453184	-1.269062958	-1.197004047
chr11	96105640	96106060	-0.001452728	-1.08430322	-1.365726795
chr12	78267220	78267740	-0.001452479	-1.023335171	-1.244128653
chr17	78316220	78316660	-0.001452152	-0.803255643	-1.084355219
chr1	48667560	48668480	0.001452049	-1.184290146	-0.861638411
chr20	30200580	30201000	0.001451538	-1.288097153	-0.995581488
chr13	76396660	76397140	-0.001451053	-1.031777562	-1.257354025
chr17	4848860	4849120	0.001451049	-1.061595294	-0.867375196
chr8	113422180	113423360	-0.001450939	-1.052578959	-1.286778373
chr1	24155640	24155980	-0.001450486	-0.947979925	-1.179026099
chr5	26398300	26398860	-0.001450461	-1.041689955	-1.297952841
chr12	20285040	20285740	-0.001450398	-0.889075099	-1.179602588
chr10	134525560	134526840	0.001449831	-1.095191503	-0.823486752
chr20	22064020	22064860	-0.00144933	-0.941853607	-1.233429485
chr11	67168540	67169700	-0.001449187	-1.002380249	-1.17815177
chr8	71421940	71422420	-0.001448553	-1.154813275	-1.283103378
chr5	28358080	28358580	-0.001448197	-1.083497656	-1.383220814
chr20	8661420	8662000	0.001447998	-1.254621848	-1.11761289
chr12	53764580	53764800	0.001447718	-1.160800893	-0.951709383
chr6	129521060	129521960	0.001447011	-1.215210198	-1.110390849
chr21	22894220	22894720	0.001446442	-1.115063746	-1.060620103
chr5	180525640	180525860	-0.001446173	-1.107995153	-1.261877829
chr21	31220940	31221300	-0.001445959	-0.670730744	-0.873282366
chr8	18089920	18090440	-0.001445796	-1.021375422	-1.224146089
chr8	18089900	18090460	-0.001445796	-1.021375422	-1.224146089
chr6	56410920	56411400	-0.001445142	-1.065548407	-1.236419738

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr9	75298460	75298840	-0.001445019	-0.799324809	-1.037004953
chr14	72849700	72850100	0.001444724	-1.12560354	-0.991099741
chr14	102783200	102783920	0.001444485	-1.197051008	-0.955558498
chr5	128045820	128046260	-0.001444098	-0.934893852	-1.123086227
chr1	196405980	196406580	-0.001443933	-1.036160396	-1.275033934
chr1	9598920	9600340	0.001442292	-1.208993616	-1.042789413
chr19	44258320	44260080	0.001442146	-1.154231312	-0.977252017
chr8	50801120	50801580	-0.00144212	-1.111680243	-1.410326996
chr8	69109740	69110240	-0.001442079	-0.987559133	-1.184285447
chr5	110582780	110583300	-0.001441858	-0.846224046	-1.164782254
chr20	57210800	57211460	-0.001441573	-0.999155381	-1.123556055
chr2	66889860	66890360	-0.001441539	-1.024515115	-1.175857133
chr19	911960	913660	0.001441268	-1.147326368	-0.919746804
chr5	110582720	110583420	-0.001441093	-0.887349195	-1.180446107
chr11	97131260	97132440	0.00144096	-1.154024344	-1.063311025
chr7	124790000	124790520	-0.001440616	-0.977370407	-1.187837391
chr12	6978640	6978860	0.001440447	-1.241565028	-1.160925104
chr12	6978640	6978860	0.001440447	-1.241565028	-1.160925104
chr7	8450820	8451320	-0.0014404	-0.882830077	-1.122160353
chr9	14739220	14739800	-0.001439649	-0.780324743	-1.061710966
chr7	80221300	80221740	-0.001439148	-0.933107002	-1.232555112
chr14	24583600	24585160	0.001438536	-1.243858703	-0.978927937
chr6	168613080	168613600	0.001438284	-1.277384236	-1.00190447
chr2	71080140	71080640	-0.001437913	-0.970395423	-1.285020682
chr17	49197380	49198680	0.001437327	-1.155343837	-0.899600959
chr7	49197440	49198620	0.001437327	-1.155343837	-0.899600959
chr9	131901140	131902080	0.001437055	-1.172346402	-0.908594655
chr20	4129260	4130100	0.00143691	-1.254283936	-0.990141228
chr5	141348280	141349040	0.001436809	-1.29142018	-1.089501336
chr13	21803220	21803780	-0.001436269	-1.137762142	-1.266820797
chr20	34790660	34791220	0.001435952	-1.376240648	-1.004264362
chr17	57183580	57184540	0.001435757	-1.133741475	-0.926299035
chr2	135487200	135487680	-0.001435496	-0.960178861	-1.221580838
chr6	84764060	84764630	0.001435309	-1.184279779	-1.023412004
chr1	247357580	247358040	-0.001435265	-0.92656584	-1.135862679
chr7	80188800	80189720	0.001435023	-1.116782899	-0.865673204
chr14	23797280	23797580	0.001434722	-1.291123338	-1.006354108
chr1	69124780	69125160	-0.001434095	-0.953603504	-1.249627712
chr3	32163080	32163360	-0.001433972	-1.163899138	-1.316414167
chr3	32163080	32163360	-0.001433972	-1.163899138	-1.316414167
chr6	31514440	31516140	0.001433455	-1.30990742	-1.12545764
chr22	46672460	46672940	-0.001432298	-0.967638256	-1.204866004
chr8	145023260	145023600	0.001432248	-1.151761228	-0.934194815
chr11	24009020	24009420	0.00143149	-1.265999979	-1.069878982
chr8	33443600	33444160	-0.001431292	-1.045479484	-1.203318618
chr11	92204940	92205280	-0.001430293	-0.996356364	-1.248748418
chr2	31956480	31957120	-0.001429798	-1.067426775	-1.327695239
chr19	41916460	41917180	-0.001429537	-0.821184499	-0.972993066
chr9	121152420	121153200	-0.001429223	-0.785180073	-1.070028907
chr19	33165160	33167220	0.001428439	-1.2480865	-1.058694995
chr16	81040020	81041300	0.001428263	-1.105410891	-0.831945342
chr4	122735120	122735500	0.001427907	-1.010177589	-0.957741006
chr1	204600240	204600620	-0.001427541	-0.997704897	-1.261934087
chr6	43930780	43931960	-0.001427272	-1.060502919	-1.342740463
chr21	34099600	34100720	0.00142687	-1.063303221	-0.768099332
chr17	53585600	53586000	-0.001426044	-0.920800909	-1.173235562
chr17	53585600	53586000	-0.001426044	-0.920800909	-1.173235562
chr5	159448880	159449180	0.001425616	-1.268049499	-1.069049708
chr6	23568080	23569680	0.001425026	-1.12011808	-1.007228888
chr8	113385020	113385440	-0.001424976	-0.855915281	-1.133291201
chr11	115271140	115271620	-0.00142442	-1.112793849	-1.363570955
chr10	17085860	17086520	-0.001423974	-0.971226971	-1.292948286
chr4	39844200	39844760	-0.001423522	-0.981667814	-1.120456886
chr18	62856740	62857420	-0.001423295	-0.913676561	-1.153148869
chr11	20937040	20937480	-0.001423287	-1.070806489	-1.220806589
chr1	9598760	9600380	0.001423112	-1.319543499	-1.124535897
chr15	34393500	34394640	0.001423083	-1.172589843	-0.964421223
chr2	179273140	179273740	-0.001422873	-1.041715874	-1.239121085
chr3	163004500	163005220	0.001422459	-1.091567251	-0.937053418
chr10	57700180	57700660	-0.001421578	-0.982335674	-1.219539089
chr20	57210860	57211440	-0.001421443	-1.020576279	-1.10921861
chr20	23058060	23058460	-0.001420908	-0.996443138	-1.090931829

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr7	17026200	17026660	-0.001420824	-0.961183416	-1.227205225
chr10	114939320	114939820	-0.00142052	-1.015180481	-1.157198591
chr3	10052680	10053060	0.001420484	-1.304906348	-1.114127584
chr4	158915600	158916000	-0.001420065	-0.956466198	-1.205735274
chr7	6565960	6566500	0.001419863	-1.251097039	-1.02392748
chr8	108294440	108295060	-0.001419464	-0.922802751	-1.188869781
chr8	20939500	20939900	0.001419351	-1.056603132	-1.009865537
chr4	14965620	14966040	-0.001419152	-0.934125722	-1.227453006
chr17	44018780	44019300	0.001418991	-1.126556697	-0.837622655
chr12	62653660	62655020	0.001418711	-1.291403376	-1.05281487
chr11	23113060	23113620	0.001418482	-1.346379145	-1.171493841
chr9	139760140	139761300	0.001418002	-1.052439998	-0.815831972
chr12	727140	727720	0.001417526	-1.257843816	-0.932831755
chr1	234613960	234615140	0.001417281	-1.325499724	-1.044191673
chr8	144922240	144923820	-0.001417161	-0.994231659	-1.12944699
chr6	80239520	80240240	-0.001417142	-0.805744676	-1.171411612
chr3	37216920	37218840	0.001416595	-1.362492434	-1.013081819
chr8	120628100	120628480	-0.001416478	-0.887303837	-1.107368745
chr7	125857620	125858020	-0.001416366	-0.920762362	-1.244478805
chr2	199713260	199713480	-0.001416301	-1.083999512	-1.26220219
chr2	199713260	199713480	-0.001416301	-1.083999512	-1.26220219
chr7	90657180	90657420	-0.001416088	-0.804383784	-1.067714775
chr3	162976300	162976840	-0.001416029	-0.996533318	-1.300459866
chr8	63124060	63124380	-0.001415919	-0.957853254	-1.2683195
chr8	63124060	63124380	-0.001415919	-0.957853254	-1.2683195
chr6	75939660	75940240	-0.001415915	-1.063813977	-1.345312033
chr8	37978620	37979140	-0.001415714	-1.085497143	-1.26725493
chr18	19375000	19375540	-0.001415491	-1.118723093	-1.35096958
chr18	19374940	19375600	-0.001415491	-1.118723093	-1.35096958
chr7	48100500	48102840	0.001415215	-1.101118635	-0.933520726
chr4	148076060	148076400	0.00141453	-1.090595906	-1.016160424
chr4	17655320	17655780	-0.001414156	-0.977619828	-1.103257433
chr12	65284720	65285000	0.001413928	-1.313716929	-1.056675065
chr2	53106420	53106920	0.001413818	-1.110185559	-1.028157633
chr8	113385040	113385380	-0.001412555	-0.869549381	-1.149969307
chr4	148964560	148965160	-0.001412413	-1.030597057	-1.28869264
chr4	109420320	109420760	-0.001412363	-0.972208959	-1.163528984
chr15	98407560	98408000	-0.001412162	-0.865293509	-1.08355857
chr10	22650560	22651380	-0.001412075	-0.995064147	-1.273080312
chr5	127290240	127290740	-0.001411643	-1.033452296	-1.249648455
chr7	3868420	3868640	0.001411491	-1.102256008	-0.87101027
chr18	41401120	41401520	-0.001411382	-1.042273342	-1.143872934
chr18	41401120	41401520	-0.001411382	-1.042273342	-1.143872934
chr22	37882300	37882620	0.001410839	-1.085344734	-0.84308942
chr5	83984700	83985380	0.001410285	-1.079939961	-0.93037352
chr17	48228200	48228700	0.001410191	-1.246729449	-1.065953415
chr3	6169200	6169640	-0.001410027	-1.123560491	-1.322969849
chr3	6169180	6169660	-0.001410027	-1.123560491	-1.322969849
chr9	132123380	132123760	-0.001409972	-0.820399837	-0.902447314
chr11	64614620	64614900	0.001409908	-1.374892427	-1.16767682
chr12	39315960	39316440	0.001409544	-1.220473696	-1.163055245
chr22	38447860	38449100	0.001409382	-1.102082895	-0.87988093
chr8	88914140	88914640	-0.001409273	-1.040023607	-1.337792506
chr1	68819900	68820420	0.001409153	-1.202082916	-1.20655864
chr4	112963580	112964020	-0.001409124	-1.125074428	-1.304117926
chr19	796620	798320	0.001408806	-1.192750729	-1.050926439
chr16	57054160	57054720	-0.001408786	-0.894753751	-1.032170398
chr2	141730320	141730880	-0.001408756	-1.040660464	-1.240655253
chr9	24718040	24718300	0.001408529	-1.036652293	-0.94552991
chr9	24718040	24718300	0.001408529	-1.036652293	-0.94552991
chr1	20129240	20129640	-0.001408518	-0.771397684	-0.999596249
chr20	31735000	31735420	0.001408172	-1.129089968	-0.995483757
chr20	31735000	31735420	0.001408172	-1.129089968	-0.995483757
chr2	40511260	40512000	-0.001408059	-0.917736495	-1.226681044
chr5	105658300	105659200	-0.001407732	-0.893250838	-1.218153684
chr3	42632040	42632700	0.001407621	-1.318026205	-1.128200004
chr18	7269140	7269660	-0.001407341	-1.00272068	-1.256239719
chr1	28652100	28652360	-0.0014073	-0.920339857	-1.120063721
chr1	105627420	105627900	-0.001406653	-0.910979314	-1.20163367
chr17	7253520	7253940	0.001406617	-1.029406197	-0.878261006
chr12	95610720	95611780	0.001406497	-1.309990938	-1.118393218
chr12	92078620	92079320	-0.001405895	-1.131879565	-1.344294041

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr17	35849220	35850560	0.001404265	-1.249521768	-1.044667639
chr19	10652160	10652400	0.001404236	-1.073348052	-0.88315584
chr19	10652160	10652400	0.001404236	-1.073348052	-0.88315584
chr14	24603180	24603380	-0.001404214	-0.932814267	-1.16721229
chr10	101988520	101990160	0.001404203	-1.173163605	-0.938567057
chr2	9606140	9606780	0.001404154	-1.28939094	-1.039262289
chr3	179899280	179899700	-0.001403989	-1.202277883	-1.341157683
chr9	131533760	131534440	-0.001403669	-0.745372125	-0.872696377
chr5	21886460	21886880	-0.001402982	-0.927205812	-1.228153052
chr10	64511020	64511620	-0.001402639	-0.997971755	-1.286118535
chr7	28698360	28698800	0.001401793	-1.054345706	-0.957470843
chr7	150223680	150224060	-0.00140142	-1.021948126	-1.174420708
chr2	65282800	65284160	0.001401368	-1.350461992	-1.119430097
chr6	52058840	52059340	-0.001401329	-1.06240472	-1.372139348
chr1	27814140	27814420	-0.001401039	-1.034303744	-1.267867917
chr6	108615880	108616260	0.001400701	-1.313962923	-1.108830504
chr10	50213740	50214140	-0.001400374	-0.917986302	-1.210939527
chr22	37988520	37988860	0.001400342	-0.979629603	-0.782125006
chr2	220507240	220507580	0.001399322	-1.251010037	-0.987816005
chr20	31073040	31073300	0.001398961	-1.212125518	-1.024226352
chr20	31073040	31073300	0.001398961	-1.212125518	-1.024226352
chr11	126350640	126350960	0.001398955	-1.316781596	-1.0691452
chr1	115052820	115054560	0.00139887	-1.24302352	-1.017085637
chr5	1464560	1466120	0.001398359	-1.209136152	-0.973261816
chr15	69168200	69168480	0.001397166	-1.211547586	-1.041502958
chr15	69167760	69168920	0.001397166	-1.211547586	-1.041502958
chr15	41196220	41196520	0.001397132	-1.275110882	-1.072756509
chr4	33132120	33132980	-0.001397098	-1.088758379	-1.282301703
chr4	15651640	15651880	0.001396644	-1.2115196361	-0.888042658
chr18	75876940	75877560	-0.001395974	-1.12077355	-1.30540413
chr9	74137300	74137760	0.001395614	-1.062534127	-0.903283333
chr7	117018940	117019460	-0.0013956	-0.999827986	-1.200493479
chr19	3500560	3501360	0.001395356	-1.170157942	-1.004839106
chr14	62228360	62229640	-0.001395116	-0.988181343	-1.101410265
chr9	137203000	137203660	-0.001395034	-0.85287308	-1.137485975
chr2	210300480	210300900	-0.001394775	-0.822939099	-1.11338811
chr12	92812440	92813120	-0.001394759	-1.029704631	-1.197826576
chr17	65082620	65082960	-0.0013942	-0.898528771	-1.11643665
chr15	34330540	34331680	0.001393966	-1.060040027	-0.777810521
chr21	20687320	20688240	0.001393525	-1.078145418	-0.92490548
chr8	93719820	93720320	-0.001392571	-0.94603442	-1.256998287
chr19	52281160	52281480	0.001392544	-0.946245878	-0.759667435
chr18	12883020	12884740	-0.001392184	-1.158029845	-1.295429931
chr4	64508880	64509280	0.001392046	-1.266990232	-1.151628124
chr1	11301780	11302080	0.001391637	-1.055830354	-0.829858283
chr5	18179240	18179660	-0.001391105	-0.880002182	-1.183985349
chr18	61089100	61090520	0.001390894	-1.345779867	-1.155386025
chr7	118731700	118732100	0.001390853	-1.26484642	-1.154994433
chr4	74987260	74987600	-0.001390743	-1.106026431	-1.364325547
chr2	174828280	174830300	0.001390348	-1.37732452	-1.149178971
chr4	152020140	152021240	0.001389875	-1.353849805	-1.116192327
chr9	115123620	115124340	0.001388858	-1.02086417	-0.871903262
chr1	22378500	22379940	-0.001388453	-1.05848813	-1.109885477
chr7	36833340	36833620	0.001388065	-1.118493796	-0.933766634
chr21	26682220	26682660	0.001387847	-1.001041457	-0.763779612
chr18	58091440	58092100	0.001387661	-1.285788722	-1.222160364
chr8	1949440	1951440	-0.001387074	-0.997324697	-1.082452649
chr1	79707920	79708320	-0.001386868	-0.956334207	-1.170790223
chr7	43138260	43139100	0.001386813	-1.195896657	-1.01174043
chr4	88928200	88929780	0.001385695	-1.213731867	-0.978622408
chr11	27947340	27947760	-0.001385563	-1.054534289	-1.250132947
chr7	36833320	36833600	0.001385526	-1.165084131	-0.93963394
chr7	1390660	1390940	0.001385523	-1.168140291	-0.992314721
chr3	50275360	50275640	0.001385145	-1.283073904	-1.087182745
chr3	50275360	50275640	0.001385145	-1.283073904	-1.087182745
chr5	4261280	4261700	0.00138464	-1.087081463	-1.00726854
chr2	80210160	80210500	-0.001384615	-0.773960987	-1.052492446
chr8	4926560	4927220	-0.001384477	-0.895124945	-1.23201143
chr6	95667660	95668020	-0.001384174	-0.955532913	-1.164276169
chr16	50785720	50786100	0.001383302	-1.03997329	-1.021055468
chr19	30515940	30516380	-0.001383142	-0.914385056	-1.152705586
chr17	74732500	74734340	0.001381748	-1.176281586	-1.028416461

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr21	18222620	18223000	-0.001381457	-0.821102575	-1.14683259
chr21	18222580	18223040	-0.001381457	-0.821102575	-1.14683259
chr3	102126020	102126520	-0.001381314	-1.170943478	-1.388357471
chr18	69398520	69399120	-0.001381107	-1.026037327	-1.303520372
chr4	112174840	112175360	-0.001380984	-1.080024031	-1.25117999
chr19	39894380	39894760	0.00138074	-1.135273219	-0.915994813
chr20	633140	634660	0.001380563	-1.216577301	-1.057627746
chr1	221376840	221377120	0.001380447	-1.254192871	-0.999779602
chr4	124842860	124843420	-0.00138036	-0.831265011	-1.096510314
chr16	1967960	1968680	0.001380161	-1.139479932	-0.941985333
chr16	77709660	77709940	0.001379958	-1.031924234	-0.84593696
chr8	138777400	138777820	-0.001379562	-0.917040517	-1.11393177
chr12	107463140	107463720	-0.001379413	-1.102007	-1.391834578
chr6	123258620	123259140	0.001379125	-1.111890673	-1.018834023
chr9	82358160	82358860	-0.001379059	-0.947595313	-1.215009876
chr10	135349920	135350620	0.001379046	-1.306997631	-1.105880955
chr5	122827980	122828380	-0.001379043	-1.075763098	-1.264998149
chr5	122827940	122828420	-0.001379043	-1.075763098	-1.264998149
chr8	144371480	144371800	-0.001378696	-1.044557284	-1.07981843
chr16	30675540	30675960	-0.001378674	-0.890872903	-1.107056602
chr14	64413060	64413600	-0.001378657	-0.938630477	-1.19686456
chr7	121180380	121180960	0.00137851	-1.188367613	-1.121494632
chr10	6244620	6245620	-0.001378452	-0.974425388	-1.056896455
chr19	42774840	42775120	0.00137843	-1.015677133	-0.863981322
chr11	64126420	64126820	0.001378393	-1.301041481	-1.059474665
chr4	57844840	57845160	0.001378342	-1.356482211	-1.134110814
chr17	29248620	29249840	0.001377993	-1.17513259	-0.833363173
chr4	148964600	148965160	-0.001377801	-1.039555427	-1.268851977
chr2	205916960	205917400	-0.001377785	-1.08947245	-1.219320488
chr11	436665300	43666240	0.001376303	-1.255220504	-1.052299627
chr12	109676040	109676380	-0.001375161	-0.998813503	-1.249981053
chr4	177826140	177826520	-0.001374558	-1.133858347	-1.284246377
chr20	34359540	34360500	0.001374538	-1.271998413	-1.060734276
chr1	194368220	194368640	-0.001374502	-1.031097563	-1.25308583
chr4	148139140	148139700	-0.001374132	-0.955031871	-1.24496481
chr2	111435360	111436260	0.001374063	-1.2637367	-1.041268475
chr6	147465980	147466360	-0.001373216	-0.964674523	-1.191023597
chr4	48768800	48769240	-0.001372619	-0.940273659	-1.138253162
chr16	82619660	82620020	-0.001371914	-0.873791946	-1.176127601
chr5	147328420	147328880	0.001371375	-1.105696082	-1.064672648
chr5	147328420	147328880	0.001371375	-1.105696082	-1.064672648
chr18	63867220	63867640	-0.00137128	-0.937479136	-1.197192744
chr8	1052060	1052500	-0.001371146	-0.880381406	-1.185085078
chr8	143700900	143701280	0.001370599	-1.063327124	-0.794127559
chr14	21979280	21979820	0.001369894	-1.281376685	-1.114977926
chr18	40519840	40520540	-0.001369881	-0.992585509	-1.146131137
chr6	24053980	24054580	-0.001369841	-1.049498294	-1.243628441
chr17	33390560	33390940	0.001369839	-1.09615754	-0.857897005
chr19	53934900	53935380	0.001369638	-1.080103462	-0.952295239
chr19	1132040	1132460	0.001369575	-1.050683515	-0.852998451
chr19	42774860	42775120	0.001369412	-1.015677133	-0.871636552
chr1	89121260	89121840	0.001369373	-1.120048994	-0.939202077
chr13	20534280	20534600	0.001369218	-1.319030802	-1.159566119
chr19	8643660	8643900	0.00136888	-1.223272643	-0.955529062
chr19	8643660	8643900	0.00136888	-1.223272643	-0.955529062
chr2	180737200	180737540	0.001368706	-1.347163165	-1.146246188
chr6	134273780	134274880	0.001368152	-1.371551308	-1.14177632
chr3	163306520	163307200	-0.001367991	-0.98362702	-1.209726796
chr12	128179520	128180060	-0.001367361	-1.022296672	-1.333919784
chr13	60942080	60942620	-0.001367133	-1.140120157	-1.392979325
chr5	83984780	83985380	0.001366703	-1.210737106	-1.045709022
chr11	23652740	23653380	-0.001366239	-0.993937615	-1.217956902
chr2	172165500	172165940	-0.001366207	-1.068962821	-1.303482538
chr2	172165460	172165980	-0.001366207	-1.068962821	-1.303482538
chr7	79111580	79112920	0.001365946	-1.161358212	-0.956257004
chr20	59202460	59202900	-0.001365896	-0.930048326	-1.233267571
chr12	59966300	59967060	-0.001365763	-1.113728244	-1.356505689
chr5	18346420	18346880	0.001365051	-1.181038877	-1.12151889
chr5	18346420	18346880	0.001365051	-1.181038877	-1.12151889
chr4	48768720	48769280	-0.001364976	-0.956602105	-1.123992339
chr13	105945880	105946320	0.001364651	-1.057838733	-1.044229525
chr17	32729660	32730140	0.001364483	-1.0372551	-0.90864129

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr19	3134060	3134480	0.001364346	-1.144172402	-1.01392409
chr17	7259340	7259660	0.001363859	-1.068050112	-0.895377914
chr2	146589040	146589720	-0.001363331	-1.082423734	-1.317247143
chr2	146589020	146589760	-0.001363331	-1.082423734	-1.311670217
chr20	22064020	22064880	-0.001363143	-0.959462091	-1.233429485
chr15	68737140	68737700	0.001362971	-1.115970777	-0.941993762
chr8	92081840	92083160	0.001362849	-1.288162225	-1.122110844
chr1	168008580	168009200	-0.001362421	-0.925099398	-1.243894609
chr6	34359680	34360800	0.001362381	-1.32512074	-1.091187799
chr11	74112520	74114040	-0.001362032	-1.038819151	-1.331366414
chr19	7598860	7599140	0.001361847	-1.060105219	-0.846272736
chr2	55844300	55845480	0.001361819	-1.329658438	-1.12453105
chr2	55844320	55845460	0.001361819	-1.329658438	-1.12453105
chr1	25869860	25870800	0.001361591	-1.19380012	-0.937448541
chr11	18752520	18752920	-0.001361558	-0.920899097	-1.173382972
chr2	80143480	80143760	-0.001361495	-0.958338297	-1.133049582
chr9	37632760	37633100	-0.001361492	-0.680371256	-0.927338301
chr18	63487100	63487480	0.001360871	-1.152668916	-1.046153015
chr16	67840100	67841100	0.001360742	-1.128530974	-0.932277515
chr19	4606720	4607120	0.001360228	-1.045286544	-0.85738392
chr7	27224320	27225160	0.001360014	-1.188553677	-1.034370768
chr19	54663120	54663900	0.001359854	-1.306030593	-1.121304315
chr16	30197260	30197480	0.00135985	-1.151529401	-0.919270673
chr3	32006820	32008100	-0.001359679	-1.111055729	-1.318816863
chr15	75337100	75337320	0.001359641	-1.062825833	-0.874498008
chr2	166809880	166810900	0.001358899	-1.222562804	-1.030568927
chr22	37852940	37854160	0.001358801	-1.096330419	-0.85894679
chr1	182050660	182051140	0.001358731	-1.238100596	-0.972486144
chr2	113484320	113484620	0.001358646	-1.288499472	-1.043970142
chr11	71935840	71936260	0.001358093	-1.175568356	-0.985007481
chr11	77122860	77123200	0.001357799	-1.215806937	-0.923072708
chr10	78386740	78387260	-0.001357619	-1.143229332	-1.300892449
chr20	8661480	8661960	0.001357599	-1.311471423	-1.17237025
chr12	8261160	8262040	0.001357047	-1.418430104	-1.165340936
chr11	25594200	25594660	-0.001356757	-1.090754329	-1.310046629
chr11	25594160	25594700	-0.001356757	-1.090754329	-1.310046629
chr2	155483120	155483620	-0.001356548	-0.94388862	-1.154744009
chr2	65282740	65284160	0.001356194	-1.331816042	-1.115052001
chr14	86785360	86785740	-0.001355817	-1.094177579	-1.238315143
chr10	103590200	103591240	0.001355058	-1.233078858	-1.020990768
chr16	50247880	50248180	0.001355021	-1.100330818	-0.866723894
chr3	172050360	172050620	0.001354733	-1.187048071	-1.024632875
chr6	159524900	159525780	0.001354555	-1.341420118	-1.090183948
chr6	48801500	48801960	-0.001354194	-1.004621519	-1.178752487
chr4	188507000	188507300	-0.001354517	-0.972275547	-1.127629037
chr17	7119060	7119400	0.001354125	-1.100826443	-0.890140198
chr1	38461660	38462040	0.001354046	-1.030720325	-0.830444837
chr12	24123580	24123900	-0.001353951	-0.878301091	-1.127834164
chr3	90123360	90124180	-0.001353838	-0.725314423	-1.085024883
chr8	137838320	137838940	-0.001353729	-1.052531526	-1.289785671
chr19	46498120	46499160	0.001353716	-1.118638072	-0.927099087
chr21	42281540	42282020	-0.001353629	-0.707547049	-0.982208789
chr3	187459220	187460120	0.001353451	-1.240461069	-0.998531483
chr3	82514840	82515480	-0.001353233	-0.992436082	-1.26367929
chr12	96792900	96794560	0.001352738	-1.259479932	-1.020526095
chr22	39264920	39265160	0.001352667	-1.209576351	-1.035369622
chr2	193856260	193856660	-0.001352336	-0.888598031	-1.145666253
chr10	78784740	78785260	0.001351901	-1.140360496	-1.007896781
chr5	153824800	153826400	0.001351821	-1.369053351	-1.093884851
chr2	119981080	119982260	0.001351724	-1.194302564	-0.990532858
chr21	32137880	32138360	-0.001351471	-0.884537286	-1.169485625
chr17	56608700	56610060	0.001351358	-1.134531372	-0.896232574
chr14	74148080	74148540	0.001351011	-1.185388906	-1.075980358
chr14	74148080	74148540	0.001351011	-1.185388906	-1.075980358
chr4	141444740	141445840	0.001350972	-1.341203802	-1.056815677
chr19	19143680	19145260	0.001350965	-1.113741368	-0.893447116
chr6	51603620	51604140	-0.001350669	-0.962955585	-1.264836177
chr6	51603620	51604140	-0.001350669	-0.962955585	-1.264836177
chr13	87431620	87432060	-0.001350202	-0.946013701	-1.098717063
chr9	81430580	81430960	-0.0013501	-0.737387806	-0.931518536
chr21	40423900	40424760	0.001350086	-1.122938688	-1.01755153
chr4	83251940	83252500	-0.001349064	-1.018057392	-1.233911312

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr2	146472520	146473020	0.001349029	-1.205062661	-1.105902508
chr14	43283920	43284420	0.001349025	-1.2219218	-1.173752967
chr17	73458880	73459600	-0.001349021	-0.927863761	-1.149504077
chr1	45958860	45959100	0.001348891	-1.231839966	-1.019652724
chr14	41362880	41363520	-0.001348609	-1.10016125	-1.286934046
chr4	68253480	68253980	-0.001348605	-1.104577917	-1.305891347
chr11	107304400	107304820	-0.001348602	-1.035703151	-1.243556396
chr1	200276360	200277260	0.00134856	-1.324381347	-1.063146901
chr14	96806240	96806720	0.00134851	-1.096591265	-1.062879113
chr9	74895620	74896400	-0.00134827	-0.866005855	-0.947487745
chr12	6934480	6935400	0.0013476	-1.315800051	-1.108251521
chr5	22978560	22978980	-0.001347579	-0.908231069	-1.177997364
chr15	41954020	41954240	0.00134748	-0.983393877	-0.685353631
chr4	55903820	55904260	-0.001346999	-0.950771984	-1.203295399
chr13	55712860	55713300	0.001346836	-1.160233476	-1.028248922
chr8	50317540	50318340	-0.001346549	-0.988790284	-1.223773385
chr4	177689420	177689860	-0.001346535	-1.041932744	-1.18976041
chr10	123617960	123618340	-0.001346171	-1.043097638	-1.246541133
chr14	24583660	24584580	0.001346139	-1.078441254	-0.914829471
chr4	159455840	159456320	-0.00134608	-0.925345672	-1.144045602
chr4	91851840	91852560	-0.001345485	-0.915428309	-1.102155348
chr2	88990400	88991700	0.001345429	-1.397344431	-1.142716165
chr17	74814220	74814680	-0.001345117	-0.972530244	-1.216395238
chr2	83004940	83005280	-0.001345081	-0.77965316	-1.055227221
chr19	5084160	5084900	-0.001345071	-1.02653112	-1.307259418
chr6	104085560	104086000	-0.001344201	-1.04579216	-1.30180522
chr3	166003280	166003780	-0.001344149	-1.013959104	-1.233695797
chr20	5591080	5591940	0.001344032	-1.310445459	-1.072561696
chr13	83178060	83178480	0.001344023	-1.190423111	-1.146212696
chr9	27061500	27061840	-0.001343884	-0.730620743	-0.994503451
chr9	27061460	27061880	-0.001343884	-0.730620743	-0.994503451
chr9	28797100	28797540	0.001343767	-1.0618885855	-0.943308738
chr17	38115240	38115560	0.001343642	-1.250522442	-1.02793554
chr3	36342180	36342420	0.001343619	-1.330667886	-1.132117306
chr3	36342180	36342420	0.001343619	-1.330667886	-1.132117306
chr6	150180280	150180740	-0.001343476	-0.941673652	-1.11759458
chr6	150180280	150180740	-0.001343476	-0.941673652	-1.11759458
chr1	182698680	182699400	0.001343029	-1.187440504	-1.108205382
chr10	30874100	30874940	-0.001342943	-0.993036599	-1.254220041
chr4	131463500	131463980	-0.001342861	-1.095239844	-1.287403945
chr4	121914660	121915160	-0.001342684	-1.048646538	-1.323801607
chr3	64016060	64016960	0.001341679	-1.329704154	-1.126579752
chr4	123500820	123501180	-0.001341189	-0.814847888	-1.08892918
chr8	84332580	84333160	-0.00134069	-1.065920653	-1.24613645
chr18	41940160	41940540	-0.001340536	-1.170841394	-1.384289587
chr13	35337420	35337740	-0.001340479	-0.909611025	-1.098214753
chr14	57729040	57729640	-0.00134018	-1.059231883	-1.239369142
chr6	42981320	42982220	0.001339871	-1.44867681	-1.25590291
chr7	81508260	81508680	-0.001339814	-1.059714248	-1.29359973
chr2	22551520	22551960	-0.001339535	-1.104522911	-1.358976957
chr2	22551460	22552020	-0.001339535	-1.104522911	-1.358976957
chr7	95488060	95488420	-0.001339345	-1.007565243	-1.228295528
chr2	203499380	203500840	0.001339203	-1.094955791	-0.915433647
chr11	42516180	42517200	0.001338899	-1.17140976	-1.12809252
chr11	42516100	42517280	0.001338899	-1.17140976	-1.12809252
chr15	65127620	65128600	0.001338809	-1.118308896	-0.960963415
chr15	89448020	89448300	0.001338732	-1.12351811	-0.870887538
chr3	72127520	72127960	0.001338665	-1.123986273	-1.11273914
chr5	83371540	83372020	-0.001338436	-0.956208821	-1.084031138
chr8	14803320	14803760	-0.001338431	-1.153032236	-1.352478681
chr8	14803320	14803760	-0.001338431	-1.153032236	-1.352478681
chr6	122719800	122721400	0.001338379	-1.247759621	-0.969594588
chr2	40859180	40859680	0.001338353	-1.11800176	-1.088857299
chr14	75412960	75413500	0.001338171	-1.257612577	-1.037755983
chr1	246885720	246885920	-0.001338119	-0.934636258	-1.164707597
chr1	246885720	246885920	-0.001338119	-0.934636258	-1.164707597
chr2	156026840	156027340	0.001337801	-1.101130937	-1.041368457
chr2	156026780	156027400	0.001337801	-1.101130937	-1.041368457
chr8	37766480	37766780	-0.001337404	-0.919010263	-1.125946261
chr16	27165920	27167100	0.00133689	-1.168889976	-0.865584815
chr4	103681520	103682820	0.001336574	-1.320543247	-1.13457801
chr5	172260620	172262000	0.001336558	-1.292717779	-1.003359235

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr8	79075080	79075760	-0.001336359	-0.973000909	-1.248915475
chr8	12873520	12874080	0.00133503	-1.193659981	-1.18372906
chr12	86891460	86892000	-0.001334855	-1.039053415	-1.273029689
chr12	48099160	48100640	0.00133397	-1.294913869	-1.133889164
chr17	73584880	73586200	0.001333901	-1.147835135	-0.946531125
chr4	149879000	149879380	-0.001333868	-0.923536129	-1.189214669
chr8	16682360	16682880	-0.001333586	-1.025095406	-1.206943863
chr14	105944940	105945400	0.001333306	-1.278204773	-1.037494372
chr20	48400860	48401180	-0.001333217	-0.948598807	-1.204478906
chr18	9471420	9471740	-0.001333029	-1.063420329	-1.278019644
chr18	9471420	9471740	-0.001333029	-1.063420329	-1.278019644
chr2	99265620	99266500	0.001333014	-1.385612061	-1.152527639
chr1	68231820	68232120	0.001332952	-1.183308391	-0.968120791
chr13	59313000	59313400	-0.001332861	-1.201748877	-1.366562486
chr16	17566420	17566860	-0.001332488	-0.954833802	-1.112991686
chr3	59303780	59304580	-0.00133198	-1.084644813	-1.315623296
chr3	42601420	42601940	-0.001331913	-0.953820146	-1.236461889
chr21	45138180	45140460	0.001331867	-1.121633314	-0.885512297
chr1	17362980	17363460	-0.001331712	-0.948047635	-1.204239766
chr2	135487220	135487640	-0.001331656	-1.012930525	-1.245758822
chr20	40898640	40899180	0.001331267	-1.318406454	-1.088476591
chr21	47705680	47706740	0.001331255	-1.166379731	-0.972981064
chr3	106588000	106588760	-0.001331065	-0.971377575	-1.289266059
chr1	44404760	44405160	0.001330931	-1.252277472	-1.022005356
chr1	44404740	44405180	0.001330931	-1.252277472	-1.022005356
chr12	71122160	71122500	-0.001330302	-0.983488155	-1.225947093
chr12	71122160	71122500	-0.001330302	-0.983488155	-1.225947093
chr2	237399380	237400080	-0.001330044	-1.049482428	-1.261147655
chr8	144371460	144371840	-0.001329313	-1.042876842	-1.070868259
chr13	92031620	92032140	-0.001329081	-1.134007736	-1.307718622
chr12	81528840	81529400	-0.001328992	-1.076575822	-1.331735575
chr9	105583960	105584460	0.001328469	-1.044515546	-0.856661879
chr2	194182040	194182460	0.001327922	-1.092839989	-0.942010532
chr19	31839760	31842020	0.001327402	-1.167347055	-0.927302039
chr6	163828960	163829440	-0.001327378	-0.925920774	-1.125158452
chr3	50230100	50230340	0.001327194	-1.320041414	-1.028085562
chr5	21183240	21183660	-0.001327112	-0.949662807	-1.229371255
chr12	59966340	59967040	-0.001327041	-1.128510364	-1.356505689
chr20	277760	278760	0.00132697	-1.100525544	-0.944035741
chr2	166377040	166377560	-0.001326899	-1.09000418	-1.291051131
chr19	58911720	58913540	0.001326812	-1.072918267	-0.914477684
chr10	78398720	78399400	-0.001326529	-1.129511977	-1.296077271
chr20	30200620	30201000	0.001325682	-1.288097153	-1.042281593
chr14	102605460	102606860	0.001325602	-1.359107749	-1.144386105
chr7	143594020	143594400	0.00132552	-1.224425702	-1.072354061
chr19	34083620	34084040	-0.001325057	-0.785604617	-1.120769312
chr19	34083560	34084100	-0.001325057	-0.785604617	-1.120769312
chr9	83608540	83609140	-0.001325013	-0.967690566	-1.156628921
chr5	109421820	109422880	-0.001324838	-1.129550448	-1.308210415
chr19	1132060	1132460	0.001324816	-1.055310739	-0.887830248
chr4	35221900	35220160	-0.00132467	-1.226216225	-1.378968304
chr2	41437800	41438220	-0.001324431	-0.818000051	-1.108581135
chr2	41437760	41438260	-0.001324431	-0.818000051	-1.108581135
chr12	39830080	39830460	-0.001324398	-0.970122535	-1.179886756
chr12	39830060	39830480	-0.001324398	-0.970122535	-1.179886756
chr8	34540240	34540660	0.001324286	-1.158750859	-1.090214641
chr15	53931460	53931940	-0.001324258	-0.835245912	-1.100917288
chr3	29371120	29371660	-0.001323883	-0.951372873	-1.277541302
chr19	1240180	1240680	0.001323881	-1.071752044	-0.927323105
chr9	76289320	76290500	-0.001323525	-0.939572646	-1.241455334
chr15	68132320	68133160	0.001322775	-1.159878813	-0.926296891
chr15	68132320	68133160	0.001322775	-1.159878813	-0.926296891
chr9	81536740	81537060	-0.001322593	-0.842517377	-1.051962394
chr10	110674500	110674960	-0.001322533	-0.846317479	-1.215737707
chr7	13472900	13473780	-0.001322455	-0.890585019	-1.241797953
chr16	4380340	4380600	0.001322249	-1.104163131	-0.896018656
chr8	135724600	135725940	0.001322218	-1.296897905	-1.163747465
chr16	69165800	69166800	0.001321576	-1.119612466	-0.906726525
chr2	62026640	62027040	-0.001321491	-0.952686299	-1.213581304
chr2	20246320	20246720	-0.001321426	-1.153647563	-1.343929615
chr21	35287660	35288620	0.001321241	-1.093279805	-0.905417067
chr2	3605380	3606520	0.001320426	-1.398672353	-1.164054674

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr12	116648140	116648600	-0.001319745	-0.956053682	-1.165480062
chr1	106331620	106332300	-0.001319711	-0.765343674	-1.055787691
chr17	3817100	3817500	0.001319593	-1.202126886	-0.961289506
chr17	3817120	3817480	0.001319593	-1.202126886	-0.961289506
chr13	31773380	31775200	0.001319544	-1.428005136	-1.147594108
chr20	18879060	18879980	-0.001319184	-0.853223732	-1.131172959
chr8	79794760	79795420	0.001318949	-1.296933798	-1.216100716
chr2	5482620	5483420	-0.001318873	-1.08442778	-1.313628643
chr6	41316680	41317140	-0.001318769	-0.833621028	-1.141838604
chr21	29165820	29166240	0.00131848	-0.927249815	-0.849905424
chr9	25047700	25048200	-0.001317898	-0.883036954	-1.098042263
chr1	219107240	219107720	-0.001317664	-0.897939105	-1.175577513
chr1	219107220	219107740	-0.001317664	-0.897939105	-1.175577513
chr22	50320420	50320740	0.00131759	-1.14220886	-1.016834299
chr22	50320420	50320740	0.00131759	-1.14220886	-1.016834299
chr6	32939040	32940300	0.001317557	-1.23306365	-1.056580107
chr16	3257080	3257340	0.00131745	-1.018501732	-0.864570962
chr16	3257080	3257340	0.00131745	-1.018501732	-0.864570962
chr4	156301200	156301740	0.001317315	-1.235922928	-1.125747031
chr17	27090780	27091060	0.001316947	-1.217515286	-0.996660487
chr12	93834900	93836500	0.001316591	-1.204392909	-0.926503578
chr19	19302820	19303860	0.001316484	-1.088525495	-0.979091605
chr2	77951980	77952460	0.001316219	-1.321945478	-1.069616564
chr10	110069460	110069880	-0.001315991	-0.966245391	-1.13570794
chr10	10248260	10248780	-0.00131554	-1.027567024	-1.305772631
chr15	36887380	36887720	-0.001315497	-0.724012652	-0.939766164
chr15	36887320	36887780	-0.001315497	-0.724012652	-0.939766164
chr19	7598820	7599160	0.001314399	-1.060046837	-0.848358722
chr20	37091800	37092060	-0.001314308	-1.152278142	-1.379276535
chr20	37091800	37092060	-0.001314308	-1.152278142	-1.379276535
chr10	6244600	6245680	-0.001314085	-0.958685818	-1.028434024
chr3	142359880	142360300	-0.00131372	-1.052777423	-1.304601441
chr2	5482700	5483360	-0.001312779	-1.105794132	-1.338355641
chr7	135723020	135723480	-0.001312726	-0.811213966	-1.055492619
chr1	160576920	160577240	0.001312401	-1.07051367	-0.87224719
chr3	71704740	71705180	-0.001312366	-1.143610589	-1.352120657
chr3	71704680	71705240	-0.001312366	-1.143610589	-1.352120657
chr13	63370820	63371380	-0.001312219	-1.174511533	-1.412890997
chr8	143813460	143813800	-0.001312081	-1.06163822	-1.259531539
chr19	38826160	38827840	0.00131163	-1.158106041	-0.928661013
chr17	26971700	26972460	0.001311612	-1.151608812	-0.917755058
chr7	10433120	10433520	-0.001311431	-1.027492204	-1.294246218
chr20	23976580	23977100	-0.001311324	-1.006513639	-1.296331723
chr20	23976580	23977120	-0.001311324	-1.006513639	-1.301941171
chr4	5104520	5104880	-0.001311311	-0.984340726	-1.059054375
chr4	6213200	6213680	-0.001311264	-1.105072304	-1.312401558
chr15	49484460	49484940	-0.001310936	-0.877531769	-1.104705062
chr18	33552100	33553040	0.001310366	-1.315179517	-1.16956243
chr4	104709400	104709800	-0.00130991	-1.124520443	-1.286339644
chr8	76581940	76582420	-0.001309484	-0.941065078	-1.187757735
chr19	14675020	14675540	0.001309479	-1.191928147	-1.008301132
chr16	84629260	84629640	0.001309043	-0.989626383	-0.89985445
chr7	146781500	146782120	0.001308874	-1.234056111	-1.192068314
chr2	73297800	73299420	0.001308731	-1.280682818	-1.092192324
chr11	45201740	45202820	0.001308639	-1.400565937	-1.14817463
chr19	55752300	55752720	0.001307075	-1.120173417	-0.883083769
chr19	55752300	55752720	0.001307075	-1.120173417	-0.883083769
chr8	22461500	22462840	-0.001306911	-1.096908346	-1.203883626
chr7	2652260	2653380	0.001306788	-1.157115654	-0.928349038
chr16	47467540	47467920	-0.001306524	-0.8700122	-1.138902496
chr1	244553000	244553480	0.001306421	-1.182332107	-1.104044084
chr2	71272240	71272440	0.001306319	-1.136117074	-1.13953805
chr2	71272240	71272440	0.001306319	-1.136117074	-1.13953805
chr4	112736960	112737420	-0.001306249	-1.097918782	-1.281823184
chr4	68166780	68167260	0.001306165	-1.163921257	-1.054787703
chr4	68166780	68167260	0.001306165	-1.163921257	-1.054787703
chr2	71080160	71080600	-0.001306128	-0.978343857	-1.278900978
chr10	104670540	104671160	-0.001306085	-0.978626804	-1.269192841
chr4	137816460	137816880	-0.001305861	-0.869783338	-1.083453591
chr14	47469240	47469860	-0.001305856	-1.031601482	-1.306997664
chr8	90277960	90278500	-0.001305774	-1.102991723	-1.329571023
chr11	64889040	64890200	0.001305623	-1.331200551	-1.098743647

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr4	57844860	57845180	0.001305494	-1.356482211	-1.145652104
chr6	47786900	47787380	-0.001305315	-1.034722685	-1.271108525
chr21	28959700	28960480	0.001305266	-0.994256901	-0.978827622
chr13	49421340	49421840	0.001305157	-1.214999108	-1.075348026
chr5	64183960	64184520	-0.001304033	-0.978457109	-1.345760555
chr14	56514080	56514700	-0.001303945	-1.191612692	-1.368542649
chr11	47395500	47395760	0.001303904	-1.213686575	-1.012514385
chr8	19519400	19519780	0.001303857	-1.31174065	-1.049073971
chr16	48643260	48645140	0.00130372	-1.221202001	-1.084262331
chr12	121142360	121142780	-0.001303418	-0.888986044	-1.143324091
chr19	14485940	14486200	0.001303165	-1.054676599	-0.914090585
chr1	76539680	76541040	0.001303087	-1.262324103	-0.985759734
chr1	67171800	67172280	-0.001302376	-0.979968119	-1.248994764
chr3	57002200	57002560	-0.001302325	-1.006503436	-1.185209422
chr1	241206660	241207220	-0.001302162	-0.880551227	-1.195420178
chr5	94694920	94695400	0.001301998	-1.20092746	-1.010735018
chr7	30323560	30324420	0.001301995	-1.307176917	-1.086009872
chr7	30323560	30324420	0.001301995	-1.307176917	-1.086009872
chr3	57839680	57840000	-0.001301787	-1.040855825	-1.245525854
chr11	2909660	2909920	0.001301374	-1.403051073	-1.168607778
chr12	14762320	14762700	-0.001301263	-0.953534304	-1.241921061
chr17	42083180	42083520	0.001300387	-1.044454819	-0.837307777
chr8	4627560	4628020	-0.001299589	-0.952029771	-1.254692408
chr22	30782580	30783940	0.00129911	-1.135823051	-0.973387732
chr16	52809520	52810040	-0.001298984	-0.861366966	-1.148845897
chr17	54132720	54133100	-0.001298896	-0.879729773	-1.108348829
chr17	54132700	54133120	-0.001298896	-0.879729773	-1.108348829
chr6	143885060	143885640	-0.001298668	-1.107194295	-1.259849239
chr19	45594740	45595440	0.001298473	-1.083618699	-0.953092028
chr7	92485140	92485900	-0.001298307	-0.871192657	-1.131029423
chr17	48100580	48102840	0.001297979	-1.102055457	-0.995433424
chr19	18223820	18224100	0.001297892	-1.175656334	-0.966289682
chr3	57134160	57134440	0.001297728	-1.230145374	-1.07559375
chr16	65499600	65500400	0.001297678	-1.106701084	-1.041442934
chr6	38271400	38272040	0.001297662	-1.229058217	-1.055245122
chr15	91072500	91074160	0.001297529	-1.113694697	-0.786806223
chr12	50793680	50795560	0.001297268	-1.222239955	-1.060864783
chr17	8062140	8062400	0.001297146	-1.227811679	-0.937886561
chr10	6877500	6879820	0.001297053	-1.117979152	-1.116624246
chr5	10284140	10284420	0.00129661	-1.276544527	-1.019011878
chr11	127867900	127868440	-0.001296432	-1.062473067	-1.253776676
chr7	117844320	117844800	-0.00129642	-0.985750662	-1.196186411
chr19	3500540	3501360	0.00129635	-1.170157942	-1.0042955
chr11	67416840	67417600	0.001296047	-1.164174423	-0.917436398
chr13	66344920	66345260	-0.001295883	-1.040551176	-1.25096276
chr4	76745800	76746340	-0.001295588	-1.151691728	-1.366314839
chr22	24407040	24408380	0.001295119	-1.085620769	-0.895622566
chr13	57279460	57279900	0.001295119	-1.1971191	-1.021741915
chr6	43477460	43478720	0.00129503	-1.236151695	-1.126489387
chr6	43477440	43478740	0.00129503	-1.236151695	-1.126489387
chr20	60169480	60169440	-0.001294192	-1.054450479	-1.190425091
chr18	1515500	1515980	-0.001294095	-1.164057504	-1.376724616
chr4	35219560	35220440	-0.001293902	-0.964840364	-1.166275402
chr21	40423900	40424740	0.001293844	-1.101936399	-1.009798398
chr8	78432180	78432580	-0.001293082	-0.872288505	-1.160412742
chr19	2274860	2275060	0.001292595	-1.020878332	-0.820019056
chr4	76745800	76746360	-0.00129253	-1.111383728	-1.352762707
chr12	17439420	17439940	-0.001291814	-0.999596076	-1.274256691
chr1	230451140	230452180	-0.001291787	-0.91335764	-1.138156476
chr2	175632500	175633280	-0.0012914	-1.130051739	-1.374818129
chr2	175632440	175633340	-0.0012914	-1.130051739	-1.374818129
chr2	140850480	140850920	-0.001291361	-0.958269921	-1.151242831
chr4	89575300	89575960	-0.001291305	-0.95736932	-1.210125675
chr15	81768840	81769220	-0.001291209	-0.730681343	-1.091486076
chr7	128045080	128046600	0.001290998	-1.164157417	-0.970100598
chr10	74451080	74452940	0.0012909	-1.222194545	-0.967573571
chr11	66313080	66313960	0.001290715	-1.24316175	-1.043456304
chr3	151478700	151479240	-0.00129064	-1.125162179	-1.288002369
chr16	20991320	20991760	-0.001290433	-0.9593695834	-1.253234655
chr10	36017800	36018380	-0.001289367	-0.995362914	-1.275556179
chr22	33589740	33590180	0.00128922	-1.034523341	-1.012950301
chr2	160118140	160118640	-0.001288878	-1.080487195	-1.266191268

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr4	36486360	36486920	-0.001288775	-1.151604028	-1.358812173
chr4	187531580	187532040	-0.001288539	-1.101431149	-1.374132177
chr17	78866680	78867520	0.001288437	-1.203402246	-1.062333336
chr5	33521300	33521780	-0.001288261	-1.094412265	-1.239263432
chr18	9073560	9073960	0.001288085	-1.349469458	-1.179110074
chr2	22141280	22141680	-0.001288031	-0.826821589	-1.058211527
chr3	102408980	102409480	-0.001287926	-1.083894983	-1.265122814
chr4	116904540	116905040	-0.001287493	-1.1204411788	-1.29780412
chr8	16546560	16547060	0.001287435	-1.314627447	-1.074215993
chr12	124938080	124938400	0.001286695	-1.110642205	-0.858991761
chr4	173704380	173704820	-0.001286129	-0.915479126	-1.216759685
chr9	81430600	81430960	-0.001285704	-0.770062208	-0.949038586
chr19	51250960	51251400	0.001285697	-1.151890493	-1.068231229
chr20	48544960	48545820	0.001285538	-1.327836372	-1.121111056
chr19	59068940	59069140	0.001284232	-1.048288591	-0.824270571
chr1	33721460	33722580	0.001284105	-1.299042437	-1.125156356
chr18	27174640	27174980	-0.001284101	-1.158265416	-1.362409758
chr16	66784960	66786380	0.001284006	-1.226350518	-1.01523537
chr11	133304520	133304960	-0.001283843	-0.944481226	-1.141906787
chr2	40859140	40859740	0.001283836	-1.123099451	-1.126433063
chr1	51655160	51655420	0.001283459	-1.153238488	-0.991550334
chr1	51654840	51655740	0.001283459	-1.153238488	-0.991550334
chr20	40898680	40899180	0.001283275	-1.31585831	-1.096192554
chr12	7000080	7000640	0.00128323	-1.411501585	-1.21780598
chr20	31070540	31071820	0.001283143	-1.305393319	-1.068631483
chr1	19387640	19388100	0.001282937	-1.080744281	-0.869917209
chr7	64908100	64908540	-0.001282705	-0.94950974	-1.259278372
chr15	46005060	46005680	-0.001282663	-0.885169482	-0.967734746
chr6	31461580	31461860	0.00128217	-1.336795862	-1.160489579
chr7	5566480	5566800	-0.001282145	-0.958179657	-0.990987423
chr3	1684440	1684780	-0.001281931	-1.039141821	-1.181793812
chr3	1684440	1684780	-0.001281931	-1.039141821	-1.181793812
chr3	159545740	159546580	0.001281586	-1.232729383	-1.098260273
chr11	65819420	65820100	0.001281394	-1.401058782	-1.149252603
chr12	40104880	40108320	0.001281263	-1.311410791	-1.20316178
chr2	22912600	22913120	-0.001281214	-1.117969782	-1.301766344
chr4	147629260	147629780	-0.001281211	-1.02470363	-1.210860164
chr10	129442940	129443420	-0.0012811	-0.890262345	-1.055939438
chr4	112174880	112175340	-0.00128092	-1.030131209	-1.194877522
chr4	187469780	187470160	-0.001280758	-0.981053	-1.185261221
chr11	127040400	127040740	0.001280554	-1.110806093	-1.029387833
chr11	127040400	127040740	0.001280554	-1.110806093	-1.029387833
chr7	12100200	12100620	-0.001280491	-1.054417102	-1.274860683
chr5	62500540	62501100	0.001279837	-1.029326733	-0.848386487
chr2	196290720	196291140	-0.001279808	-1.072610865	-1.316131384
chr13	60942040	60942640	-0.00127929	-1.159408007	-1.381910577
chr14	81453360	81454580	0.001279209	-1.215216539	-1.010806801
chr19	49149520	49150400	0.001279136	-1.107068873	-0.929547947
chr19	49149500	49150420	0.001279136	-1.107068873	-0.929547947
chr8	140699380	140700380	-0.001279007	-1.014487817	-1.24079654
chr22	50294960	50295420	0.001278724	-0.996408589	-0.861007455
chr15	69780880	69781300	-0.001278661	-1.041170821	-1.250551368
chr7	6387900	6388860	0.001278589	-1.215546473	-0.9836575
chr9	25940100	25940840	-0.001278564	-0.954189014	-1.194255559
chr9	25940100	25940860	-0.001278564	-0.954189014	-1.194255559
chr12	69226900	69227540	-0.00127844	-1.034440078	-1.277957507
chr16	4673940	4675520	0.001277993	-1.215373073	-1.049611704
chr16	14726080	14727340	0.001277992	-1.156842618	-0.968604281
chr19	18042820	18044240	0.001277916	-1.12521708	-1.017926904
chr15	59312140	59312580	-0.001277671	-0.829882809	-1.143492704
chr12	80908080	80908900	-0.001277659	-0.960296076	-1.240996523
chr19	42721140	42722980	0.001277107	-1.045359678	-0.852000391
chr6	48668760	48669020	-0.001276936	-0.837116503	-1.027600909
chr7	155725060	155726120	0.001276912	-1.225667874	-1.081692045
chr16	67839880	67841420	0.001276871	-1.280805007	-1.130034717
chr19	4553500	4553940	-0.001276684	-0.953115313	-1.030425014
chr7	73963540	73963840	-0.001276409	-0.885431421	-1.108147271
chr9	11474100	11474460	-0.00127603	-0.619695541	-0.847380491
chr11	131035680	131036240	0.001275503	-1.026717185	-1.059415096
chr8	19370740	19371200	-0.001275483	-0.982561343	-1.20723539
chr12	56211220	56212440	0.001275231	-1.355596222	-1.141956193
chr22	30649240	30649620	0.001275214	-0.861995753	-0.702630276

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr10	4708420	4710600	0.001275167	-1.341761952	-1.155741605
chr10	4708420	4710600	0.001275167	-1.341761952	-1.155741605
chr11	122932460	122933840	0.001275033	-1.348702691	-1.129935226
chr1	28198820	28199260	0.001275012	-1.253418012	-1.099542543
chr10	32143740	32144260	0.001274936	-1.30243442	-1.093214105
chr15	75337020	75337380	0.001274742	-1.005047082	-0.86619503
chr13	66286160	66286500	-0.001274596	-1.009303162	-1.293037145
chr4	57073700	57074200	-0.001274312	-0.979461732	-1.178620645
chr20	12374220	12375060	-0.001273711	-0.954279479	-1.26283386
chr19	50391560	50391900	0.001273627	-1.028481343	-0.807615732
chr2	157292380	157293100	0.001273552	-1.203006212	-0.970321864
chr4	173704260	173704880	-0.001273107	-0.937422555	-1.238563288
chr11	1245540	1246040	0.001272944	-1.220443359	-0.940293464
chr13	64464520	64465140	-0.001272415	-1.030895687	-1.241261125
chr8	37978760	37979080	-0.001271992	-1.067229463	-1.261335966
chr9	79821940	79822420	0.001271889	-1.148613894	-1.070662061
chr9	79821820	79822540	0.001271889	-1.148613894	-1.070662061
chr9	91932580	91932880	0.001271663	-1.003379663	-0.774008558
chr3	61236420	61238020	-0.00127146	-1.025605667	-1.146197803
chr1	60551460	60551780	-0.001271335	-0.95262197	-1.17798082
chr16	7944280	7945340	-0.001271237	-0.882901337	-1.147992716
chr2	161405360	161405680	-0.001270947	-0.822785843	-1.122437279
chr12	128179500	128180100	-0.001270513	-1.036360168	-1.335091218
chr13	101625560	101626380	0.001270426	-1.151009963	-0.986227271
chr11	7044280	7045040	-0.001270299	-1.018223556	-1.279936486
chr7	75676880	75677820	0.001270238	-1.197224217	-1.047331758
chr7	75676880	75677820	0.001270238	-1.197224217	-1.047331758
chr15	98109300	98109840	-0.001270035	-0.769743145	-1.033030436
chr5	171615060	171616480	0.001270001	-1.272395651	-1.085752148
chr6	67086540	67087120	-0.001269749	-0.997517463	-1.301752124
chr9	28470720	28471120	-0.001269624	-0.761322592	-1.038136946
chr6	90538880	90540180	0.001269532	-1.394738755	-1.152285047
chr16	46722560	46723980	0.001269468	-1.112462125	-0.905036132
chr5	117479440	117480120	-0.001269418	-1.019492606	-1.237150864
chr2	157291920	157293540	0.001269108	-1.199126875	-0.949470215
chr12	125347760	125349220	0.001269012	-1.13943172	-1.053745238
chr1	97707480	97707940	-0.00126881	-0.940127053	-1.191639252
chr19	51842080	51844060	-0.001268728	-0.919222715	-1.053188579
chr1	57830380	57831240	-0.001268697	-0.856779923	-1.188725088
chr11	110518640	110519220	-0.001268634	-1.056695387	-1.265587733
chr16	70380440	70380940	0.001268532	-1.208754045	-1.046545202
chr1	60164480	60165720	0.00126851	-1.290743745	-1.081272302
chr2	69613740	69615120	-0.001268478	-1.138226147	-1.243653208
chr4	14965580	14966120	-0.001267951	-0.919422472	-1.208815247
chr3	1750180	1750440	-0.001267888	-0.958717158	-1.240067021
chr11	123000120	123000640	-0.001267506	-0.988111775	-1.260570358
chr15	85523560	85525740	0.001267395	-1.093254197	-0.931984395
chr15	34634480	34636200	0.001267379	-1.012959297	-0.825940186
chr22	26824900	26826160	0.001265403	-1.131892947	-0.977327163
chr1	153721420	153722700	0.001264638	-1.187718191	-1.053573406
chr7	64411680	64411960	0.001264353	-1.142852792	-0.949682405
chr6	152895120	152895520	-0.001264293	-0.951453887	-1.143466695
chr6	44306300	44306580	0.001264237	-1.2579505848	-1.039484106
chr13	26463200	26463580	-0.001264029	-1.028591147	-1.201346805
chr15	92395960	92397860	0.001263841	-1.259405351	-1.014104196
chr16	81109900	81111300	0.00126357	-1.087925681	-0.822613139
chr10	49590680	49591140	-0.001263432	-0.948836514	-1.16454218
chr8	50616300	50616780	0.001263417	-1.182113453	-0.974727771
chr21	46408120	46408560	0.001263313	-0.919030905	-0.69503189
chr5	143339020	143339320	-0.001263304	-1.041919741	-1.234962456
chr7	90404760	90405180	-0.001262709	-0.992343025	-1.087412563
chr7	149194160	149195280	0.001262682	-1.224420023	-0.966535154
chr10	107562200	107562820	-0.001262667	-0.928936431	-1.260321314
chr20	32441280	32441760	-0.001262497	-0.755845944	-0.962959144
chr7	87998220	87998740	0.001262443	-1.183334704	-1.055361427
chr19	854520	854880	-0.001262377	-0.951933522	-1.168786733
chr6	100266180	100266880	0.001262376	-1.264846181	-1.05234604
chr6	100266160	100266700	0.001262376	-1.264846181	-1.05234604
chr2	40511220	40512000	-0.001262334	-0.957973882	-1.243798709
chr6	7140920	7141940	0.001262041	-1.371067329	-1.153991038
chr2	221892840	221893100	0.001261565	-1.098176788	-0.983711072
chr2	221892840	221893100	0.001261565	-1.098176788	-0.983711072

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr1	229323720	229324200	0.001261468	-1.141041527	-1.021295504
chr2	25193980	25195260	0.001261359	-1.321753108	-1.162604746
chr7	41982660	41982980	0.001261288	-1.217749676	-0.971127316
chr3	22572040	22572480	-0.001261266	-1.080904277	-1.357455367
chr15	52121180	52122540	0.001261095	-1.173848185	-0.958198146
chr4	15893700	15894220	-0.001260738	-1.042972612	-1.224678812
chr20	34787400	34788280	0.001260703	-1.102360759	-0.919195351
chr19	13212460	13212820	0.001260587	-1.049746447	-0.949849156
chr21	37441220	37443420	0.001260279	-1.109895572	-0.929222103
chr5	53809980	53810340	-0.001260047	-1.140075294	-1.334488909
chr2	40005980	40007060	0.001260026	-1.277736439	-1.007502049
chr12	102091120	102092100	0.001259893	-1.218647169	-1.102778029
chr6	30197240	30197460	0.001259747	-1.155255761	-0.90909447
chr2	208509920	208510520	-0.001259744	-0.907191449	-1.217498111
chr1	35978660	35979120	-0.001259342	-0.892797798	-1.097099492
chr2	174798120	174798620	0.001259161	-1.32870782	-1.196069691
chr21	25755700	25756140	-0.001258903	-0.849179425	-1.039812249
chr7	74071680	74073420	-0.001258339	-1.00372973	-1.18247468
chr3	102724760	102725180	0.001258053	-1.332355637	-1.174765951
chr14	102605480	102606860	0.001257864	-1.359107749	-1.150584129
chr2	180128520	180129820	0.001257731	-1.375667277	-1.18448759
chr3	99836480	99836920	-0.001257586	-1.091024888	-1.275865249
chr8	69109780	69110180	-0.00125757	-1.003339847	-1.176544175
chr6	83407460	83408020	-0.001257531	-1.039780013	-1.215964639
chr17	78316300	78316660	-0.001257289	-0.915199094	-1.165191148
chr1	92788340	92788860	-0.001256874	-0.978907932	-1.223094092
chr11	34764800	34765340	-0.001256773	-1.05743841	-1.218534281
chr6	141693280	141693600	-0.001256655	-0.945008613	-1.166205984
chr17	1162480	1162720	0.001256594	-1.175680671	-0.937962348
chr11	41998920	419990300	-0.001256586	-1.084176232	-1.363620527
chr1	16297660	16298240	-0.001256462	-1.015828091	-1.213931435
chr15	44167400	44167680	-0.001256433	-0.918232107	-1.02471468
chr12	21653800	21655400	0.001256344	-1.273161171	-1.125178544
chr10	107852840	107853320	-0.001256286	-0.931580618	-1.174204514
chr22	32149340	32150700	0.001256204	-1.168937531	-1.005177608
chr1	16623220	16623620	-0.001256195	-1.031504034	-1.175628303
chr12	1702920	1704480	-0.001256146	-1.138590663	-1.226642757
chr3	195635680	195636860	0.001255999	-1.302663151	-1.061105759
chr3	195635580	195636960	0.001255999	-1.302663151	-1.061105759
chr8	137634240	137634740	-0.001255727	-0.898083775	-1.160119598
chr11	45167560	45169320	-0.001255341	-1.077253368	-1.213619618
chr1	66562000	66562480	-0.001255208	-0.941787698	-1.182589994
chr6	159555800	159556080	0.001255067	-1.278036076	-1.021909792
chr4	156301220	156301700	0.001254973	-1.201696977	-1.151969991
chr9	8776600	8777120	-0.001254733	-0.864464147	-1.049981038
chr2	62026660	62027040	-0.001254354	-0.969145724	-1.211937997
chr7	148663880	148664200	0.001254341	-1.268479191	-1.045635513
chr1	107379020	107379540	-0.001254241	-1.046167107	-1.265583221
chr1	231493600	231493920	-0.001254072	-0.949679023	-1.063418942
chr15	93321020	93321300	-0.001253908	-1.029505644	-1.303317593
chr15	93321020	93321300	-0.001253908	-1.029505644	-1.303317593
chr12	81528880	81529400	-0.001253905	-1.110080476	-1.356630811
chr4	109168300	109168800	-0.00125389	-1.00226486	-1.209027417
chr13	22051180	22051480	0.001253887	-1.316408478	-1.066431207
chr7	4680940	4682260	0.001253864	-1.2554475	-1.063257352
chr5	10353400	10354600	0.001253727	-1.099229169	-0.909736886
chr16	2469100	2469500	-0.001253587	-0.803466434	-0.986193322
chr9	105684400	105685020	-0.001253095	-0.973145395	-1.175999836
chr3	78303100	78303480	-0.00125286	-1.0630862	-1.273146439
chr1	23740320	23740680	-0.001252568	-0.896737506	-1.106377961
chr1	11322160	11323000	0.001252562	-1.110564748	-0.967297769
chr15	48801340	48802020	-0.001252438	-1.022796063	-1.249728777
chr12	14782740	14783680	0.001251682	-1.166413887	-0.950282534
chr22	43010480	43011460	0.00125164	-1.260097442	-1.130959223
chr22	43010460	43011480	0.00125164	-1.260097442	-1.130959223
chr10	110069440	110069880	-0.001251375	-0.966245391	-1.116068674
chr2	133873160	133873580	0.001251169	-1.171924537	-1.047197722
chr3	129345560	129345980	0.001250817	-1.156642857	-0.949521749
chr3	153169080	153169560	-0.001250797	-1.069423185	-1.260633395
chr4	21104760	21105160	-0.001250533	-1.105370683	-1.296763172
chr4	21104720	21105200	-0.001250533	-1.105370683	-1.296763172
chr8	142094440	142094740	0.001250467	-1.343389493	-1.070923982

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr8	142094140	142095040	0.001250467	-1.343389493	-1.070923982
chr4	15003500	15004200	0.001250387	-1.222529577	-1.010706727
chr3	1426160	1426680	-0.001250326	-1.016666177	-1.275658101
chr4	62872900	62873320	-0.001250275	-1.188830951	-1.332761465
chr16	68297940	68299020	0.001250057	-1.182644914	-0.975841076
chr8	24231720	24232180	-0.001250021	-0.903834781	-1.140436692
chr8	11417460	11417960	-0.001249893	-1.115809841	-1.327248465
chr1	58071720	58072900	-0.001249832	-1.126231302	-1.354325079
chr12	78982180	78983040	0.001249649	-1.313587161	-1.175770332
chr1	27021920	27024460	-0.001249089	-1.057033327	-1.110300003
chr1	27021920	27024460	-0.001249089	-1.057033327	-1.110300003
chr19	36207880	36209540	0.001248519	-1.079482477	-0.921833216
chr17	617640	618600	0.00124827	-1.29091295	-1.135504947
chr2	119802420	119802720	-0.001248003	-0.989748267	-1.200735227
chr2	119802420	119802720	-0.001248003	-0.989748267	-1.200735227
chr8	93886900	93887520	-0.001247946	-0.906968498	-1.182888868
chr3	194463320	194463700	-0.001247795	-1.087573112	-1.28846085
chr3	194463300	194463720	-0.001247795	-1.087573112	-1.28846085
chr7	48653220	48653940	-0.00124748	-0.852315824	-1.090918517
chr5	11128660	11129060	-0.001246776	-1.098840228	-1.288923551
chr21	28959780	28960420	0.001246473	-0.988834273	-0.959150289
chr6	52058840	52059300	-0.001246403	-1.094995972	-1.375163778
chr13	67564540	67564940	0.001246297	-1.138608747	-1.002708751
chr2	185337780	185338700	-0.001246217	-0.989636691	-1.251767133
chr1	145575040	145576740	0.001246158	-1.254004338	-1.006946631
chr15	90728000	90728580	0.001246102	-1.093648608	-0.816125856
chr10	11502460	11502860	0.001246002	-1.06078671	-1.026488239
chr1	60762080	60762480	-0.001245879	-0.986237259	-1.1746743
chr11	2448940	2450240	0.001245768	-1.209561951	-0.961474641
chr4	61896040	61896420	-0.001245766	-0.954014421	-1.21818172
chr4	61896000	61896460	-0.001245766	-0.954014421	-1.21818172
chr8	35445340	35445700	-0.001245031	-1.002157233	-1.215926647
chr6	15244840	15246400	-0.001244917	-1.16982519	-1.306963627
chr15	89877640	89878740	0.001244698	-1.129370054	-0.970191471
chr17	37850220	37850760	-0.001244306	-0.912654416	-1.143334405
chr14	51296720	51298460	0.001244214	-1.276310025	-1.039828922
chr20	59202440	59202900	-0.001243841	-0.910169107	-1.221768068
chr7	33605200	33605660	-0.001243559	-1.05681874	-1.199811941
chr14	100841880	100843200	0.00124308	-1.236332114	-1.024558532
chr14	77519200	77520180	-0.001243075	-0.998868234	-1.031431912
chr2	7567140	7568040	0.001242865	-1.097489207	-0.951694185
chr16	24107820	24108180	-0.001242833	-0.875289689	-1.074563384
chr4	141025300	141025760	-0.001242831	-1.126277324	-1.267357655
chr3	85650060	85650540	-0.001242596	-0.946942885	-1.189357438
chr2	73089360	73090320	0.00124136	-1.162181994	-0.919272962
chr2	73089400	73090280	0.00124136	-1.162181994	-0.919272962
chr11	3012780	3014640	0.001241229	-1.109006348	-0.98522046
chr4	980020	981540	0.00124071	-1.041603146	-0.861819793
chr4	32816800	32817340	-0.001240354	-0.947637919	-1.157929021
chr6	142956980	142957440	-0.001240167	-1.208949276	-1.393944317
chr4	184546260	184546640	0.001240138	-1.191641078	-1.065730227
chr10	17085800	17086500	-0.001239926	-1.007521171	-1.253741894
chr8	21595480	21595880	-0.001239343	-1.14675345	-1.267226754
chr1	243856380	243856780	-0.001239033	-0.993725558	-1.23402378
chr18	21491500	21492180	-0.001238922	-1.057852953	-1.336954546
chr2	194182040	194182480	0.001238578	-1.056416023	-0.91568798
chr5	12046400	12046900	0.00123841	-1.139783196	-1.074692854
chr15	72492000	72492400	0.001238261	-1.110061804	-0.847157557
chr6	80745680	80746280	0.001237728	-1.021650871	-0.962768704
chr2	43202120	43202680	0.001237318	-1.260057619	-0.998881346
chr17	29662060	29662560	-0.001237275	-0.818863155	-1.054095977
chr16	65499600	65500340	0.001236964	-1.123443894	-1.058110514
chr8	130951400	130952700	-0.00123689	-0.971161961	-1.089405497
chr11	37617920	37618480	0.001236856	-1.107037678	-1.131819582
chr10	135085720	135086040	-0.001236594	-0.869140538	-0.996978108
chr12	108154120	108155360	0.001236449	-1.265642902	-1.081869747
chr10	15204520	15205060	-0.001236422	-0.941553393	-1.17259693
chr4	148814440	148814960	-0.001236402	-1.004877845	-1.222856736
chr20	30467280	30468340	0.001236202	-1.192025969	-1.056028773
chr5	67558000	67558540	-0.001235826	-1.053267462	-1.189893452
chr8	112037040	112037440	-0.001235797	-1.014877828	-1.282090136
chr12	29913480	29914300	-0.001235735	-0.855470712	-1.21303912

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr21	23422380	23422640	-0.001235692	-0.858926608	-0.973477078
chr21	23422380	23422640	-0.001235692	-0.858926608	-0.973477078
chr19	48825040	48825560	0.001234844	-1.227374635	-1.06608124
chr19	54665920	54666280	0.001234614	-1.18750323	-1.032118493
chr19	36504260	36506340	0.001234525	-1.233700526	-1.091664129
chr7	113316740	113317220	-0.001234442	-0.733222502	-1.137536278
chr21	24493080	24493680	-0.001234306	-1.012786161	-1.212455539
chr5	117876460	117876700	0.001234057	-1.199512715	-1.118093825
chr15	101459300	101460160	0.00123392	-1.147649092	-0.969089683
chr14	82753700	82754100	0.00123242	-1.145338798	-1.126889401
chr19	34345720	34346140	-0.001232133	-0.895611935	-1.12147347
chr5	5778240	5778760	-0.001232058	-0.984095411	-1.297446159
chr13	49421320	49421840	0.001231882	-1.193771131	-1.050781794
chr8	125027600	125028040	-0.001231794	-1.010603182	-1.166037773
chr5	83337160	83337680	0.001231516	-1.147937019	-1.096044682
chr5	83337160	83337680	0.001231516	-1.147937019	-1.096044682
chr8	113355020	113355460	-0.001231449	-1.113804954	-1.335170136
chr11	94963720	94964840	0.001230729	-1.336027486	-1.051012506
chr4	115654620	115655300	-0.001230712	-0.990318859	-1.164966167
chr14	60557960	60559140	0.001230483	-1.248378928	-1.096419433
chr10	60528900	60529400	0.001230146	-1.130007101	-0.996562046
chr5	88164860	88165440	-0.00122985	-0.86815934	-1.159297628
chr20	30467400	30468160	0.001229831	-1.192025969	-1.015004785
chr12	78462220	78462580	-0.001229667	-1.047998575	-1.217034314
chr11	85779360	85781160	0.001229409	-1.397330828	-1.245990445
chr3	195148540	195149420	-0.00122904	-0.960093668	-1.154889502
chr1	175288500	175289420	0.001228768	-1.27238938	-1.008634273
chr4	184546280	184546640	0.001228739	-1.191641078	-1.068763582
chr6	82632540	82633100	-0.001228667	-1.137258197	-1.30184378
chr14	24299120	24299540	0.001228434	-1.171629468	-1.014297172
chr3	166089780	166090140	-0.001228355	-0.916302111	-1.171123213
chr2	233724900	233725380	-0.001228331	-0.851359762	-1.083915606
chr18	58091520	58092060	0.001227852	-1.1973431	-1.178113063
chr8	120628040	120628560	-0.001227599	-0.904582861	-1.114870594
chr5	53809980	53810360	-0.001227268	-1.122140036	-1.315318418
chr7	56076620	56077480	0.001227264	-1.174905274	-1.019833426
chr2	198317780	198318420	0.001226987	-1.374657418	-1.249508593
chr2	52748740	52748980	-0.001226837	-0.809806039	-1.058244098
chr2	180302340	180303040	-0.001226787	-1.123577967	-1.35103458
chr18	69631700	69632080	-0.001226515	-0.883503955	-1.144481284
chr17	70324220	70324600	-0.001226261	-0.899221231	-1.099423777
chr17	70324200	70324620	-0.001226261	-0.899221231	-1.099423777
chr8	83130600	83131140	-0.001226261	-1.002574428	-1.282177505
chr15	52068920	52069820	0.001226101	-1.098532203	-0.861044064
chr15	52068920	52069820	0.001226101	-1.098532203	-0.861044064
chr5	2623180	2623700	0.001225608	-1.123881742	-1.023094117
chr11	77408360	77408780	-0.00122549	-1.17935792	-1.392809348
chr11	77408320	77408820	-0.00122549	-1.17935792	-1.392809348
chr2	137693240	137693780	-0.00122503	-0.944149241	-1.232332636
chr16	88803140	88803420	0.001224872	-0.998621445	-0.836302108
chr4	135053820	135054760	-0.001224843	-1.148528371	-1.379962881
chr1	197962480	197963400	-0.001224771	-1.019547002	-1.294557981
chr1	225522460	225523100	-0.001224296	-0.988452591	-1.158805255
chr6	129577660	129578140	-0.001224277	-1.092813138	-1.296752235
chr6	461109840	46110420	-0.001224198	-1.040949366	-1.316641926
chr15	34330540	34331580	0.001224138	-1.011604216	-0.794166643
chr5	20356740	20357260	0.001223696	-1.182940293	-1.054085126
chr3	168428880	168429300	0.001223459	-1.290588961	-1.10371017
chr5	1545280	1546180	0.001223098	-1.136727061	-0.947375722
chr14	103584400	103584660	-0.001222904	-1.098359687	-1.197198416
chr10	74451640	74452540	0.001222337	-1.226686018	-1.036633226
chr1	228296260	228298060	0.001222216	-1.2728646	-1.16766101
chr10	8304620	8305220	-0.001222085	-1.045000204	-1.193784338
chr11	118798800	118799060	0.00122196	-1.30953162	-1.137461569
chr2	193856200	193856680	-0.001221934	-0.964767422	-1.19699076
chr4	164960940	164961840	-0.001221764	-0.995189241	-1.285572417
chr4	164960940	164961840	-0.001221764	-0.995189241	-1.285572417
chr3	182510640	182511960	0.001221681	-1.416713496	-1.257156022
chr10	103235500	103235900	-0.001221654	-1.044282655	-1.277372865
chr7	1619160	1619460	0.001221492	-1.244081246	-0.995194527
chr2	135962040	135962520	-0.001221398	-1.153836075	-1.327232836
chr2	135962000	135962560	-0.001221398	-1.153836075	-1.327232836

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr17	1370700	1371280	-0.001221326	-0.996014428	-1.166462994
chr2	170683780	170685000	0.001221137	-1.162772163	-0.92420656
chr9	77338560	77338940	-0.001221009	-0.837797991	-1.083740661
chr5	142812780	142813300	-0.001220843	-0.962802376	-1.219526606
chr11	115990080	115990820	-0.001220779	-0.909597968	-1.171677551
chr1	210500100	210500440	-0.001220333	-0.954956627	-1.143554959
chr14	102785900	102786660	-0.001220263	-1.136836769	-1.286157085
chr2	203102740	203103900	-0.00122006	-0.969674624	-1.075670569
chr3	90161160	90161640	0.001219663	-1.172918979	-1.127332233
chr11	34182000	34182480	0.00121956	-1.332214618	-1.04941521
chr19	24228940	24229400	0.001219218	-1.04198085	-0.940405427
chr8	31905640	31906140	-0.001219192	-1.017189678	-1.26694241
chr8	31905560	31906220	-0.001219192	-1.017189678	-1.26694241
chr17	2206100	2207580	0.001219076	-1.16527235	-0.989417252
chr11	33795260	33796820	0.00121902	-1.248344184	-1.015507341
chr3	80452940	80453460	0.001218823	-1.084714145	-1.025031274
chr8	11417440	11418000	-0.001218372	-1.096218728	-1.319116011
chr11	65479220	65480820	-0.001218302	-0.982650276	-1.155879345
chr17	8092540	8092860	0.001217821	-1.036922216	-0.848273617
chr2	219261400	219261740	0.001217759	-1.141817801	-0.872902401
chr1	64970800	64971780	-0.001217377	-1.068582627	-1.177948532
chr12	53614680	53615060	0.001217339	-1.125121196	-1.038935329
chr10	84955020	84955480	-0.001216471	-1.005887896	-1.143556285
chr14	64280920	64281380	-0.00121638	-1.012408808	-1.212852085
chr1	113181480	113181800	0.001216107	-1.11396219	-1.076532212
chr9	21366180	21366640	-0.001215638	-0.799671797	-1.025649014
chr2	154599260	154599760	0.001215634	-1.314598594	-1.108797972
chr20	50029340	50029740	-0.001215527	-1.072859135	-1.167005198
chr7	113316640	113317280	-0.001215409	-0.751799974	-1.121363055
chr21	21068780	21069260	0.001215213	-0.923413956	-0.865773906
chr20	47257220	47257660	0.001214853	-1.111964146	-0.942221049
chr20	37590360	37591560	0.001214737	-1.282843604	-1.157496246
chr5	55330060	55330600	-0.001214727	-0.834417876	-1.133766913
chr6	51142620	51143040	-0.001214461	-1.034405041	-1.275945136
chr6	51142560	51143100	-0.001214461	-1.034405041	-1.275945136
chr19	58330900	58331220	0.001214301	-1.080997095	-0.943600857
chr2	118571640	118572840	0.001214091	-1.220769573	-0.991634321
chr14	27232520	27232840	-0.001213784	-1.021162682	-1.237688853
chr11	59973760	59974220	0.00121368	-1.146104595	-1.014154631
chr16	70464820	70465200	0.00121346	-1.097188906	-0.912412559
chr6	2840880	2842840	0.001213386	-1.187003626	-1.020839382
chr12	97832100	97832480	-0.001213302	-0.953375581	-1.224810179
chr12	54697880	54698360	0.001213066	-1.119906636	-0.91483072
chr1	115003760	115004100	-0.001212992	-0.994538849	-1.157797212
chr13	47353680	47354100	-0.001212944	-1.045499244	-1.279028225
chr10	27015080	27015360	0.001212873	-1.228250032	-1.032648259
chr21	47731460	47732160	-0.001212617	-0.980322935	-1.055045786
chr12	89094180	89094420	-0.00121244	-1.027028168	-1.247536423
chr4	11164760	11165240	-0.001211829	-1.038335685	-1.299214695
chr4	29265820	29266600	-0.001211683	-1.13257152	-1.329896231
chr9	13710900	13711520	-0.001211636	-0.82031097	-1.058491404
chr11	16806780	16807700	0.001211606	-1.221352575	-0.880283256
chr1	198125320	198126940	0.001211498	-1.294595579	-1.089822367
chr15	49154080	49154360	0.001211221	-1.093363453	-0.82782685
chr2	185337860	185338660	-0.001211173	-0.97143687	-1.235280258
chr10	73533740	73534060	0.001210786	-1.170480968	-0.915533243
chr8	120844620	120845560	0.001210655	-1.341988445	-1.010202938
chr21	24576560	24577000	-0.001210605	-0.891622268	-1.080253565
chr15	74428680	74429080	0.001210396	-1.164200732	-0.908676589
chr2	6459560	6460100	-0.001210352	-0.998491663	-1.159085174
chr9	136703360	136704340	0.001209591	-1.017861564	-0.759138484
chr6	13892980	13893380	-0.001209436	-0.939170542	-1.277893058
chr10	111682600	111683780	0.001209054	-1.284999496	-1.137368099
chr1	8419980	8421300	-0.001208927	-0.871658824	-1.062075454
chr1	243856300	243856800	-0.001208579	-1.026389742	-1.248032019
chr16	88372600	88373580	0.001208482	-1.165362821	-1.025697893
chr6	126092800	126093220	-0.001208404	-0.94575872	-1.194077996
chr19	19051600	19052380	0.001207969	-1.239019085	-0.964019199
chr19	19051440	19052540	0.001207969	-1.239019085	-0.964019199
chr17	80681160	80681800	0.001207769	-1.141852759	-0.938696361
chr19	14228120	14229320	0.001207731	-1.305613471	-1.152804905
chr5	17600600	176001800	0.001207673	-1.257058591	-1.106470668

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr7	38368000	38368620	-0.001207579	-1.041605026	-1.288042924
chr17	7751800	7752060	-0.001207574	-0.901914986	-1.029214119
chr19	30335220	30336480	0.001207473	-1.069259459	-0.877502835
chr8	93508880	93509320	-0.001207464	-0.911554656	-1.196768897
chr17	21191080	21191760	0.001207319	-1.101621059	-0.868294246
chr22	43601800	43602600	0.001207169	-1.140369367	-0.87652587
chr6	117452920	117453500	-0.001206976	-0.963118978	-1.216508145
chr22	23714340	23715240	0.001206806	-1.116828183	-1.121903181
chr17	27053880	27054180	0.001206799	-1.265634737	-1.06124339
chr14	74959620	74961000	0.001206574	-1.429330183	-1.268459656
chr1	173760280	173760700	-0.001206171	-0.926896196	-1.148514365
chr1	173760240	173760740	-0.001206171	-0.926896196	-1.148514365
chr11	114614360	114614840	-0.001206128	-0.833584385	-1.060573345
chr1	105627380	105627920	-0.001205945	-0.896334398	-1.14153036
chr13	34116440	34117260	0.001205758	-1.342450095	-1.167756458
chr13	34116400	34117300	0.001205758	-1.342450095	-1.167756458
chr9	28425040	28425560	-0.001205599	-0.742354182	-1.005239558
chr13	54771360	54771720	-0.001205278	-1.003191182	-1.23093907
chr4	187997460	187997940	-0.001205087	-1.118643855	-1.294389273
chr7	115162700	115163160	0.001204999	-1.339030026	-1.232172328
chr21	22519740	22520360	-0.001204929	-0.820860419	-1.102227749
chr10	110075840	110076060	-0.001204207	-0.863514893	-1.18311166
chr10	110075840	110076060	-0.001204207	-0.863514893	-1.18311166
chr8	24077320	24077880	-0.001204033	-1.12952115	-1.314799374
chr18	62856700	62857480	-0.001204041	-0.935258714	-1.153148869
chr13	39030440	39030940	-0.001203971	-0.940403428	-1.083594628
chr21	17736760	17737220	-0.00120394	-0.806744724	-0.970807482
chr17	7745980	7746200	-0.001203913	-0.940500011	-1.052260744
chr19	29703600	29704360	0.001203835	-1.086074906	-1.0045817
chr6	16183400	16183640	0.00120328	-1.101015072	-0.88839328
chr10	67542120	67542560	-0.001203212	-1.013385985	-1.22649943
chr7	99005940	99006820	0.001203185	-1.207817485	-0.921019727
chr13	67564460	67564960	0.001202977	-1.171501003	-1.042427981
chr19	18528480	18528680	0.001202764	-1.032990905	-0.856041634
chr9	33024660	33025900	0.001202604	-1.184381131	-1.022054537
chr19	54919680	54920780	0.001202591	-1.270170808	-1.096662319
chr3	185006020	185006420	-0.001202328	-0.852331539	-1.107270292
chr3	185005980	185006460	-0.001202328	-0.852331539	-1.107270292
chr16	1661880	1662780	0.001202308	-1.273612253	-1.08503488
chr13	95362880	95364540	0.001202284	-1.191224466	-1.018070997
chr2	67681080	67681540	-0.001202144	-0.88942552	-1.139414448
chr3	152881180	152881420	0.001201766	-1.115171139	-0.873132894
chr3	44902840	44904000	0.001201578	-1.248934501	-1.113724575
chr2	181291460	181291920	0.001201571	-1.120400795	-1.070809981
chr16	54647040	54647680	-0.001201321	-0.75250432	-1.087478963
chr3	9978040	9978420	0.001201259	-1.16744819	-1.082596736
chr5	17812460	17812840	-0.001201093	-0.91135017	-1.065935311
chr20	633120	634660	0.001201093	-1.218610529	-1.075063977
chr2	117962340	117963180	-0.001201005	-1.11518608	-1.237301669
chr2	81297460	81297920	-0.001200998	-0.845786056	-1.149326115
chr17	37097660	37098100	-0.001200876	-0.88152282	-1.144677796
chr17	37097660	37098100	-0.001200876	-0.88152282	-1.144677796
chr6	70630480	70631160	-0.001200845	-0.98913684	-1.20579959
chr17	72489520	72489820	0.0012007	-1.239543611	-1.032240078
chr17	72489520	72489820	0.0012007	-1.239543611	-1.032240078
chr1	110182880	110183160	0.001200531	-1.300899059	-1.105708691
chr3	154851260	154851720	-0.001200142	-1.079695337	-1.221571731
chr16	46864220	46865920	0.001200072	-1.182265437	-0.968443028
chr12	5345160	53455440	-0.001200027	-0.952917171	-1.207606887
chr19	1094840	1095680	0.001199939	-1.054474012	-0.871313224
chr11	41989760	41990340	-0.00119985	-1.084176232	-1.356422789
chr8	57255680	57256240	-0.001199308	-1.140671651	-1.383641872
chr11	90968720	90969240	-0.00119922	-1.025254497	-1.318031987
chr12	40769480	40769900	0.001198906	-1.132401584	-1.072273022
chr16	66901500	66902340	0.00119872	-1.146082674	-1.007084748
chr16	66901500	66902340	0.00119872	-1.146082674	-1.007084748
chr14	96830220	96830360	0.001198625	-1.413652008	-1.209057677
chr11	46402720	46403520	0.001198254	-1.368472191	-1.173418473
chr4	69416900	69417160	-0.001197804	-1.206826006	-1.317193331
chr1	17655300	17655720	-0.001197803	-0.778013258	-1.034152628
chr9	10403020	10403460	0.001197693	-0.98988162	-0.911057544
chr8	38914660	38915060	0.001197641	-1.125497783	-1.076287175

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr8	38914640	38915080	0.001197641	-1.125497783	-1.076287175
chr2	7923820	7924340	-0.001197635	-0.98185277	-1.176862082
chr12	22763680	22764260	0.001197537	-1.216524757	-1.194092265
chr13	79056940	79057380	-0.001197525	-1.115228205	-1.21357472
chr2	179273140	179273640	-0.001197222	-1.110933584	-1.319363818
chr7	101791760	101792160	-0.001196774	-0.971198905	-1.136602889
chr7	101791760	101792160	-0.001196774	-0.971198905	-1.136602889
chr7	124130820	124131300	-0.001196579	-1.125197427	-1.292664642
chr12	53765920	53766180	0.001196474	-1.171356778	-0.900945301
chr15	98109380	98109780	-0.001196383	-0.757055245	-1.002288551
chr17	73092300	73092640	0.001196189	-1.159572842	-0.880572792
chr2	102146000	102148080	-0.001196133	-1.105352017	-1.306713786
chr21	19876980	19877240	-0.001196011	-0.825730433	-1.017447062
chr17	29814420	29815580	0.001196	-1.303400487	-1.123467166
chr2	212182400	212183040	-0.001195893	-1.002307536	-1.269967787
chr2	235018480	235018880	0.00119561	-0.985994924	-0.839009989
chr2	180357840	180358820	-0.001195075	-0.932599651	-1.078881452
chr2	180357800	180358860	-0.001195075	-0.932599651	-1.078881452
chr21	47705660	47706740	0.001194989	-1.169336392	-0.977406546
chr5	94132100	94132580	-0.001194534	-1.150123791	-1.337144713
chr6	42930780	42931240	0.0011945	-1.203549464	-0.987484698
chr10	19229780	19230460	-0.001194467	-0.960447923	-1.226065319
chr4	35200700	35201140	-0.001194133	-1.127312099	-1.290346334
chr4	35200680	35201160	-0.001194133	-1.127312099	-1.290346334
chr6	137520320	137521180	-0.001194037	-1.044209324	-1.280740993
chr1	60551140	60552040	-0.001194013	-1.105087343	-1.293150848
chr19	2270480	2270780	0.001193947	-1.127831248	-0.935318657
chr8	65170660	65171160	-0.001193798	-0.960047134	-1.129175353
chr8	113839200	113839600	0.001193051	-1.346925355	-1.270103544
chr8	113839180	113839620	0.001193051	-1.346925355	-1.270103544
chr9	132125080	132125660	-0.001193041	-1.085880252	-1.239888573
chr13	65715260	65715540	-0.001192966	-0.937563155	-1.077979258
chr2	198370360	198370620	-0.001192925	-0.926624004	-1.065313884
chr11	118964840	118966580	0.001192457	-1.269699199	-1.102087793
chr13	98628060	98629520	0.00119221	-1.324717678	-1.092043924
chr4	31331860	31332340	-0.001192183	-1.037872441	-1.209479521
chr7	26903200	26904600	0.001191973	-1.21156736	-1.091918802
chr17	30813400	30814620	-0.00119189	-1.05674441	-1.152605544
chr1	179779020	179779300	0.001191865	-1.227873789	-0.976292507
chr2	128615440	128616160	0.00119171	-1.273671637	-1.041881857
chr6	56500800	56501420	0.001191551	-1.019671547	-0.991105821
chr7	8092540	8092800	0.00119152	-1.018218671	-0.818128033
chr7	84969140	84969560	0.00119143	-1.177848808	-1.131689787
chr10	35624640	35626480	0.001190985	-1.186243438	-0.990493343
chr6	82177320	82177820	-0.001190881	-0.94629633	-1.267910115
chr16	10592100	10592560	0.001190852	-1.070248133	-0.995314852
chr2	215376400	215376800	0.001190843	-0.984899844	-0.955759673
chr3	196359180	196359880	0.001190682	-1.321825176	-1.165470865
chr10	121355740	121357700	0.001190582	-1.308272527	-1.187382596
chr7	114855400	114855920	-0.001190155	-1.119083556	-1.226173303
chr2	88957460	88957960	-0.001190123	-0.810593811	-1.023112753
chr5	13265300	13266700	-0.001189511	-1.013771797	-1.243218452
chr5	32710900	32711420	0.001189177	-1.085512423	-0.943509072
chr2	55065740	55066040	0.001189177	-1.144090399	-0.956174777
chr2	145877960	145878320	-0.001188693	-0.964885586	-1.186844406
chr19	36239100	36239880	-0.00118852	-0.750848322	-0.906264486
chr11	67416860	67417500	0.001188492	-1.123810936	-0.911067839
chr1	38147640	38148840	0.001188408	-1.154823	-0.931904496
chr10	49513860	49515380	0.001188371	-1.345423874	-1.167232208
chr9	22882040	22882560	-0.001188298	-0.855901938	-1.049158829
chr20	33291560	33293020	0.001187674	-1.193665395	-1.048082766
chr3	10289100	10290960	0.00118763	-1.300058251	-1.108756523
chr7	8198260	8199240	0.001187142	-1.225581699	-1.057200993
chr2	230156580	230157100	0.00118705	-1.139634485	-1.056813439
chr7	48243920	48244580	0.00118673	-1.30282605	-1.124964679
chr13	38609760	38610640	0.001186525	-1.15770934	-1.17570584
chr1	35978720	35979080	-0.001186242	-0.893375416	-1.072877969
chr7	68740580	68741100	-0.001186138	-1.050919334	-1.17729582
chr4	159689680	159690700	0.001185984	-1.427776411	-1.229291691
chr12	3913080	3913380	0.001185616	-1.151591676	-0.961157022
chr17	73092280	73092640	0.001185511	-1.181173326	-0.906397821
chr17	76127420	76128580	0.00118549	-1.168058075	-0.991229665

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr22	51015960	51017040	0.001185438	-0.940388765	-0.80023369
chr14	92587780	92588800	0.001185334	-1.328621012	-1.124079096
chr8	76221760	76222180	-0.001185251	-0.949271317	-1.143164195
chr12	121668140	121668380	0.001185145	-1.14871018	-0.97486945
chr13	35584660	35585120	-0.001185098	-1.067656615	-1.267223017
chr16	29801680	29802500	0.001185092	-1.118391281	-1.0247297
chr13	84125380	84126060	0.001184924	-1.271718315	-1.168909752
chr6	83854580	83855360	-0.001184551	-1.004254501	-1.255365219
chr16	84705960	84706280	0.001184505	-1.107343315	-0.993945478
chr17	8198280	8199240	0.001184501	-1.225581699	-1.051078725
chr3	12045260	12047200	-0.001184283	-1.134864826	-1.218046833
chr16	3442940	3443540	-0.001184056	-1.050657965	-1.216459836
chr6	66269940	66270440	-0.001183899	-1.11823642	-1.377301441
chr9	22411680	22412100	0.001183823	-1.212639766	-1.10737586
chr1	219102100	219102940	-0.00118363	-1.052471849	-1.305445638
chr9	138986500	138987600	0.00118339	-1.019662725	-0.828391443
chr2	123293280	123293660	-0.001183136	-1.087150118	-1.238855108
chr5	86708600	86709100	0.001182369	-1.1145563	-0.982813194
chr7	44597920	44598220	-0.001182254	-1.068588387	-1.168155356
chr9	8776580	8777160	-0.00118224	-0.8664425	-1.079186428
chr20	20438880	20439680	-0.001182217	-0.955598227	-1.162519406
chr10	83106120	83106600	-0.001182027	-1.000927804	-1.261313409
chr2	211366960	211367400	0.001181917	-1.155586841	-1.09851525
chr9	138739620	138739960	-0.00118134	-1.007159495	-1.129314591
chr14	96829240	96830400	0.001181308	-1.413652008	-1.191436619
chr3	6219940	6220380	0.001181015	-1.203103708	-1.045859112
chr3	6219900	6220420	0.001181015	-1.203103708	-1.045859112
chr2	95916420	95916960	-0.001180617	-1.002016816	-1.159933362
chr15	89448020	89448280	0.001180543	-1.111245866	-0.88909863
chr17	65821300	65822300	0.001180356	-1.062103798	-0.934075718
chr8	106884820	106885220	-0.001180096	-0.94776627	-1.195876122
chr17	44344060	44344580	-0.00118008	-0.973379838	-1.181841893
chr17	44344040	44344600	-0.00118008	-0.973379838	-1.181841893
chr21	30445680	30446360	0.001179805	-1.009936497	-0.869164799
chr1	150045100	150045380	0.001179613	-0.979298964	-0.912281131
chr4	109168300	109168740	-0.001179512	-1.048098194	-1.204064846
chr9	31663720	31664220	-0.001179192	-0.765452265	-0.994050551
chr21	24576520	24577060	-0.001179017	-0.915820206	-1.139263789
chr17	61816920	61817460	0.001178977	-1.096899985	-1.040641534
chr17	74518920	74519820	0.001178958	-1.249779958	-1.059153482
chr20	34787340	34788320	0.001178755	-1.131120795	-0.925539546
chr5	149828500	149830100	-0.001178399	-1.058882817	-1.154800097
chr19	56135380	56136180	0.001178339	-1.130879139	-0.983293139
chr19	14007040	14007660	0.001178207	-1.056615763	-0.991755151
chr2	175206260	175206560	0.00117772	-1.26946639	-1.156902665
chr2	175206240	175206580	0.00117772	-1.26946639	-1.156902665
chr1	99468440	99468800	-0.001177617	-1.031380716	-1.2406485848
chr10	104670540	104671120	-0.001177603	-1.014532474	-1.244310296
chr19	45375880	45376420	-0.001177051	-0.853545333	-1.126838819
chr4	32297480	32298160	-0.001176987	-1.211156079	-1.388273995
chr9	30080960	30081560	-0.001176736	-0.87850423	-1.088554918
chr11	1962720	1963840	-0.001176719	-0.926171512	-1.084404958
chr8	93719860	93720300	-0.001176601	-0.982082889	-1.249336564
chr4	74044940	74045440	-0.001176308	-1.108883837	-1.337501815
chr13	63316520	63316980	-0.001176206	-1.160712677	-1.37895351
chr9	127702700	127703900	0.001176172	-1.110539522	-0.871517021
chr9	105798700	105799140	-0.001175789	-0.963889346	-1.139473449
chr11	72492240	72493740	0.001175766	-1.185450973	-1.005833425
chr22	49016580	49017420	0.001175661	-1.096217079	-0.946364598
chr19	14485920	14486240	0.001175621	-1.03793287	-0.913128625
chr15	48801460	48801980	-0.001175427	-0.985259147	-1.225699074
chr16	29823220	29823640	-0.001175392	-0.88944917	-0.918133563
chr21	39079800	39080180	0.001175386	-0.88779233	-0.740492862
chr12	6480500	6480900	0.001175231	-1.373911298	-1.199836555
chr12	118214700	118215200	0.001174956	-1.107007671	-1.039492493
chr15	54018220	54018660	-0.001174727	-0.858123091	-0.990219866
chr11	30246300	30246620	-0.001174675	-0.99797602	-1.227530576
chr22	47781840	47782420	0.001174501	-1.067599388	-0.968005739
chr22	47148720	47149040	0.001174439	-0.9558882806	-0.749115328
chr19	14062560	14063940	0.001174382	-1.263817125	-1.124700433
chr6	141364480	141364960	-0.001174221	-1.171533632	-1.382523352
chr2	21649140	21649600	-0.001174084	-1.152986586	-1.371829475

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr1	72364300	72364880	0.00117384	-1.147426044	-1.117446301
chr21	21068680	21069240	0.001173833	-0.949034352	-0.937288214
chr6	141364480	141365000	-0.001173806	-1.165858059	-1.387570656
chr10	45454240	45455980	0.001173602	-1.400620717	-1.228709675
chr19	2720760	2721780	0.001173521	-1.198458328	-1.052677645
chr10	29191080	29191320	-0.001173456	-0.880129584	-1.100141935
chr10	29191080	29191320	-0.001173456	-0.880129584	-1.100141935
chr19	5719700	5721000	0.001173299	-1.142295381	-1.041133364
chr18	70891100	70891580	-0.001173241	-0.958163141	-1.144912761
chr4	15005180	15005600	0.001172937	-1.387401143	-1.245306738
chr8	67836860	67838660	0.001172846	-1.242751365	-1.051933224
chr19	1028100	1028340	0.001172764	-1.032655836	-0.897287648
chr18	31376760	31377160	-0.0011725	-1.06696631	-1.294729173
chr2	208030520	208031900	0.001172497	-1.234194465	-1.003836505
chr12	76477660	76479280	0.001172232	-1.249042033	-1.02166796
chr2	125830280	125831020	-0.001172096	-0.967915207	-1.24802433
chr6	85145360	85145840	-0.001171955	-1.047857857	-1.211797042
chr13	53902380	53903140	-0.001171859	-1.115445994	-1.309269516
chr11	118888960	118889900	0.001171352	-1.401177853	-1.201084692
chr12	6797800	6799740	0.001171047	-1.44515329	-1.271487415
chr1	194368160	19436860	-0.001170539	-1.054621545	-1.232415104
chr9	92136540	92136760	-0.001170022	-0.816691854	-0.980908363
chr9	92136540	92136760	-0.001170022	-0.816691854	-0.980908363
chr12	73863900	73864140	0.001169856	-1.243013346	-1.120962903
chr12	73863900	73864140	0.001169856	-1.243013346	-1.120962903
chr8	109905500	109906000	-0.001169787	-1.021813515	-1.232369686
chr19	56014720	56015880	0.001169768	-1.105090997	-0.944169086
chr4	104401820	104402340	-0.001169747	-1.129591013	-1.268712083
chr22	36839200	36839640	0.001169686	-0.993637237	-0.862907234
chr2	198138460	198138980	-0.001169684	-1.030770031	-1.161274136
chr11	106890580	106891080	-0.001169633	-0.876028252	-1.171019014
chr5	170480700	170481140	-0.001169136	-1.116438317	-1.315049953
chr15	93211060	93211540	-0.001168735	-0.930711249	-1.026667942
chr15	74045100	74045820	-0.001168725	-0.946514025	-1.017555228
chr1	156023020	156023840	0.001168639	-1.284439158	-0.987676655
chr19	35632000	35632540	0.001168548	-1.271783081	-1.117086311
chr1	237245640	237246020	-0.001168144	-0.963173557	-1.11635275
chr6	77489120	77489560	-0.00116813	-1.048340518	-1.247434226
chr9	29868280	29868780	-0.00116796	-0.949601447	-1.180924832
chr2	184790480	184791120	-0.001167716	-0.965104782	-1.24209538
chr6	110028360	110028840	-0.001167693	-1.108680684	-1.328584161
chr4	93398660	93399180	-0.00116759	-0.940853293	-1.147305183
chr17	80681260	80681740	0.001167535	-1.166693585	-0.937403333
chr14	63266280	63266800	-0.001167299	-1.115922387	-1.329189877
chr17	7120400	7121060	-0.001167287	-0.993549598	-1.133765649
chr1	32965740	32967020	0.001167168	-1.087923051	-0.972463632
chr13	50589000	50589500	-0.001167071	-1.111814278	-1.370030881
chr15	81927640	81927920	-0.001167014	-0.961879365	-1.15764957
chr15	81927640	81927920	-0.001167014	-0.961879365	-1.15764957
chr2	32390600	32391080	0.001166975	-1.228726322	-1.089712264
chr2	142311060	142311400	-0.001166919	-0.983710379	-1.138446928
chr9	20565940	20566160	-0.001166843	-0.983615313	-1.152319932
chr10	8304680	8305140	-0.001166815	-1.067553258	-1.232843793
chr1	228565960	228566400	0.001166762	-1.244583255	-0.981060238
chr3	180184200	180184580	0.00116668	-1.029031279	-1.066635475
chr1	29426940	29427480	-0.001166627	-1.030436308	-1.211792473
chr1	203940420	203940860	0.001166603	-1.125773431	-1.047784907
chr17	40915500	40915780	0.001166522	-1.087886311	-0.917283623
chr7	79934900	79936140	0.001166501	-1.061797578	-0.918900031
chr19	48248580	48249500	0.001166229	-1.090131986	-0.951030474
chr6	97857400	97858300	0.001166216	-1.151393244	-1.168385663
chr10	80062400	80063760	-0.00116609	-1.024552077	-1.127485587
chr16	34949840	34950160	-0.001166089	-0.908601327	-1.111679598
chr2	6439480	6440020	-0.001165853	-1.084320171	-1.276866457
chr19	31474400	31475140	-0.001165673	-0.996676593	-1.259615179
chr1	198837680	198838140	0.001165654	-0.815249712	-0.853931852
chr8	16785020	16785600	-0.001165335	-1.001383833	-1.280293615
chr17	65712940	65714660	0.001165275	-1.175244563	-0.968458987
chr2	48712860	48713400	-0.001165115	-1.029933038	-1.204973494
chr13	54080640	54081080	-0.001164734	-1.123848131	-1.261936703
chr2	188678580	188679020	-0.001164732	-0.913091148	-1.085884119
chr1	983400	983740	0.001164599	-1.151636674	-0.859750098

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr8	21936700	21936920	-0.001164542	-0.992154137	-1.151507399
chr1	199528540	199528980	-0.001164538	-0.905148786	-1.263387241
chr13	84125340	84126200	0.001164507	-1.161321722	-1.121527041
chr6	41034140	41035360	0.001163946	-1.206898496	-1.122832649
chr2	52870800	52871160	-0.001163885	-0.946863609	-1.170752029
chr1	27560560	27562180	-0.001163657	-0.979015718	-1.026154428
chr12	54718460	54719040	0.001163581	-1.440163337	-1.254659087
chr8	17103540	17105180	0.001163383	-1.29817102	-1.175196882
chr21	24615520	24616020	-0.001163347	-0.855560278	-1.135781434
chr7	105773260	105773680	-0.001163208	-0.907652348	-1.058015652
chr2	26256360	26257380	0.001162843	-1.358953895	-1.156420462
chr9	113913200	113914100	-0.001162535	-0.80978964	-1.119922917
chr15	63481240	63482500	0.001162527	-1.046714998	-0.803686236
chr5	149815240	149816440	0.001162327	-1.298756123	-1.098150517
chr11	89938080	89938340	0.001162299	-1.137671916	-0.947502677
chr7	7456480	7457800	-0.001162279	-1.058988008	-1.22145308
chr1	76539540	76541080	0.001162183	-1.182002367	-0.949140447
chr8	126444320	126444600	0.001161908	-1.273138499	-1.064536255
chr14	54192720	54193180	-0.001161794	-1.00364779	-1.235312918
chr15	66094540	66094980	-0.001161549	-0.849157162	-1.06827742
chr7	5594340	5595200	0.001161531	-1.198372624	-0.939365144
chr7	121842300	121842780	-0.001161503	-1.102154205	-1.280262089
chr5	36294700	36295280	-0.001161436	-1.024847482	-1.248431292
chr2	97001160	97002400	0.00116141	-1.340151167	-1.106800577
chr1	103219440	103219940	0.001161372	-1.156310293	-1.055402096
chr7	4680960	4682280	0.001161065	-1.235371705	-1.05767703
chr16	8921580	8922080	-0.001160979	-0.856285373	-1.096220349
chr1	173400380	173400640	0.001160814	-1.188946315	-1.048218443
chr1	173400060	173400960	0.001160814	-1.188946315	-1.048218443
chr20	32580520	32582480	-0.001160756	-1.06085479	-1.169362548
chr6	30512200	30513080	0.001160755	-1.263321596	-1.024929143
chr16	9184300	9184580	0.001160667	-1.12465124	-0.95394327
chr11	60372580	60372840	-0.001160386	-0.894082614	-1.1217568
chr21	34961060	34961500	0.001160258	-1.016462904	-0.755562528
chr3	181683100	181683700	0.001159893	-1.196836381	-1.104979824
chr21	35770040	35770560	-0.001159836	-0.908009057	-1.012960625
chr7	100340440	100340680	0.001159455	-1.221055851	-1.027761987
chr7	100340440	100340680	0.001159455	-1.221055851	-1.027761987
chr10	104263420	104264160	0.001159322	-1.23639184	-1.036876378
chr9	28479660	28480140	-0.001159284	-0.825999734	-0.993378597
chr20	23058000	23058460	-0.001159198	-1.083616082	-1.14630394
chr20	60757200	60758740	0.001159164	-1.25712566	-1.052461836
chr21	45552920	45554200	0.001158813	-1.101865625	-0.865858677
chr3	54769820	54770380	-0.001158157	-1.112168161	-1.296372658
chr8	98709300	98709580	0.001157994	-1.146682618	-1.0673386
chr2	47669060	47669620	0.00115795	-1.306146494	-1.154832926
chr2	47669060	47669620	0.00115795	-1.306146494	-1.154832926
chr14	74550400	74552440	0.001157927	-1.319432116	-1.080244258
chr3	14885500	14886000	-0.001157844	-1.252930822	-1.349997114
chr2	46843560	46844760	0.001157825	-1.267578254	-1.07105819
chr5	85677020	85677560	-0.001157778	-1.147164692	-1.414761937
chr1	17362960	17363500	-0.001157667	-0.962752449	-1.189710439
chr1	200772060	200772340	0.001157657	-1.12216908	-0.924801941
chr8	100922580	100923180	-0.00115764	-1.069832622	-1.3113692
chr2	122512300	122513820	0.001157548	-1.285328164	-1.083833534
chr5	81147200	81148500	0.001157311	-1.248715161	-1.071687249
chr15	61639940	61640720	-0.001157195	-0.973152379	-1.195932383
chr7	8065160	8065460	0.001157072	-1.076417684	-0.957658533
chr7	26903240	26904620	0.001157061	-1.17099827	-1.065759221
chr9	101896860	101897320	-0.001156841	-0.880464615	-1.064110436
chr9	96755820	96756260	-0.001156547	-0.884622736	-1.0819933
chr17	29814280	29815580	0.001156523	-1.223729984	-1.04668171
chr20	43050340	43050680	-0.00115618	-1.072718887	-1.248186933
chr6	143949860	143950340	-0.001155744	-1.028930335	-1.171581305
chr19	3985100	3985960	0.00115532	-1.254780252	-1.109181652
chr5	158639560	158639860	-0.001155023	-1.045786839	-1.229242632
chr6	57533000	57533280	-0.001155004	-0.946264886	-1.179919455
chr19	56165040	56167340	0.001154836	-1.227349805	-1.009225469
chr3	103912720	103913100	0.001154548	-1.087411468	-1.097066674
chr7	148830580	148830900	-0.001154441	-1.030407896	-1.175483978
chr1	30952040	30952740	0.001154314	-1.339983695	-1.11565532
chr8	1377960	1378440	-0.001154052	-1.054691318	-1.205925002

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr7	149019860	149020220	-0.001153828	-1.017918886	-1.270510171
chr6	33395520	33396500	-0.001153802	-1.122606036	-1.280788396
chr2	9695760	9696440	0.001153765	-1.377184761	-1.187619018
chr8	135358440	135358980	-0.001153622	-0.94290058	-1.203517823
chr2	74681800	74682320	0.001153463	-1.277226257	-1.057394607
chr19	46366120	46366760	0.001153368	-1.190477347	-1.006143671
chr19	53238160	53238560	0.00115328	-1.157818905	-0.994029112
chr17	62213780	62214080	0.001153076	-1.180513158	-1.109902111
chr17	62213780	62214080	0.001153076	-1.180513158	-1.109902111
chr2	58121100	58121580	-0.001152924	-1.140086665	-1.296845704
chr6	26740200	26740620	0.001152898	-1.272166092	-1.103000734
chr8	52717620	52718200	-0.001152865	-0.984340563	-1.107936789
chr1	36839420	36839700	0.001152862	-1.086002107	-0.923740519
chr19	38261320	38261720	-0.001152826	-0.845101719	-1.039047155
chr1	63909940	63910700	0.001152806	-1.113959747	-1.081563155
chr2	212182440	212182960	-0.001152764	-1.016185258	-1.258278331
chr19	8578380	8579280	0.001152763	-1.217373753	-1.040826891
chr15	69109820	69111320	0.00115243	-1.235872118	-1.03122407
chr19	47759600	47760900	0.001152229	-1.282941031	-1.162570256
chr2	33823880	33824980	0.001152214	-1.258830005	-0.963859515
chr22	36924800	36925760	0.001151941	-1.16641726	-1.003102165
chr22	36924440	36926120	0.001151941	-1.16641726	-1.003102165
chr12	103276140	103276700	-0.001151901	-0.949671173	-1.203309099
chr12	20303040	20303700	-0.001151738	-0.979336196	-1.214415519
chr3	31613280	31613920	-0.001151206	-1.12570122	-1.400253337
chr15	59396620	59397940	0.001151175	-1.115879175	-0.933063899
chr5	54267800	54268380	0.001151074	-1.12201684	-1.120087074
chr5	62767960	62768540	-0.001151073	-0.994029719	-1.244690302
chr3	132135820	132136940	0.001150902	-1.304900497	-1.116165873
chr2	45877720	45879060	-0.001150889	-1.147398116	-1.155134052
chr17	73774980	73776260	0.001150875	-1.205246975	-0.988614655
chr2	54013520	54014800	0.001150683	-1.269216102	-1.050751903
chr2	215039780	215040180	-0.0011505	-0.957461695	-1.191715987
chr2	215039760	215040200	-0.0011505	-0.957461695	-1.191715987
chr7	98740060	98742100	-0.001150243	-1.090907952	-1.203917474
chr7	156399120	156400560	0.001150183	-1.26632252	-1.048618147
chr5	163421000	163421400	-0.001149988	-0.813497125	-1.0338553
chr12	83032920	83033260	-0.001149777	-1.204069112	-1.403848943
chr17	27920040	27921100	-0.00114974	-0.967462682	-1.13416305
chr14	71786800	71788360	0.001149145	-1.276591654	-1.151489642
chr7	117251840	117252340	-0.001149022	-1.061645882	-1.268057562
chr19	14227980	14229360	0.001148937	-1.288324785	-1.151636523
chr8	71421960	71422420	-0.001148854	-1.192403294	-1.28360466
chr10	25830700	25831080	-0.001148789	-0.960559903	-1.198284386
chr10	25830680	25831100	-0.001148789	-0.960559903	-1.198284386
chr3	61000440	61000720	-0.001148758	-0.970930753	-1.12355145
chr1	154909020	154909940	-0.001148692	-1.115134139	-1.251517765
chr19	3135860	3136160	0.001148523	-1.119468043	-0.893894558
chr12	121084780	121085040	0.001147863	-1.228663943	-1.056367317
chr2	55276120	55276440	0.001147825	-1.196413275	-0.970594386
chr19	50094280	50094860	0.001147814	-1.067569621	-0.836827468
chr20	24937320	24937980	0.001147724	-1.349635068	-1.190116029
chr10	32545340	32546220	0.001147685	-1.184052692	-0.968772217
chr17	79790680	79791800	-0.001147604	-0.86371908	-1.131252054
chr14	27910060	27910500	0.00114721	-1.187098455	-1.142793431
chr10	87746980	87747500	0.001147081	-1.107161464	-0.887471861
chr3	115435340	115435820	-0.001146881	-1.075597564	-1.330965788
chr9	14938120	14938560	-0.001146683	-0.771741988	-0.001898368
chr3	157230860	157232240	-0.001146144	-1.101415368	-1.247849503
chr3	109698340	109699060	-0.001146139	-1.044159269	-1.347189651
chr4	135510240	135510720	-0.00114606	-1.095701736	-1.294169756
chr19	13262440	13262900	0.001145751	-1.215582025	-1.093765608
chr10	32855620	32856220	-0.001145677	-1.032092992	-1.251288351
chr10	24617740	24618500	-0.001145499	-0.896685776	-1.270081323
chr17	48228100	48228780	0.00114539	-1.18878053	-1.039673439
chr1	247553120	247554040	0.00114519	-1.234670118	-0.946174744
chr12	9246780	9247180	-0.001145179	-1.008227867	-1.213174878
chr9	109304640	109305220	-0.001145089	-0.752187211	-1.017954024
chr1	9188460	9189980	0.001144939	-1.280231811	-1.110605116
chr3	98904340	98904680	-0.001144794	-0.911784238	-1.080512948
chr5	157952120	157952640	-0.001144639	-0.952520494	-1.219433847
chr13	63226660	63227020	-0.001144586	-1.04516006	-1.22921002

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr17	80967440	80968220	0.001144541	-1.075414937	-0.850356935
chr2	26204660	26206200	0.001144314	-1.283640139	-1.050053693
chr11	70116060	70117620	0.00114388	-1.43554101	-1.258910385
chr20	4065940	4066220	0.00114381	-1.286775169	-1.165351583
chr20	4065620	4066540	0.00114381	-1.286775169	-1.165351583
chr11	105947560	105948920	0.001143779	-1.367300636	-1.137511933
chr21	45206580	45207340	0.001143374	-1.132753201	-0.956571469
chr2	237399300	237400120	-0.001142881	-1.0232320441	-1.2470809
chr7	122372460	122373180	-0.001142651	-1.019160159	-1.23577733
chr2	170681140	170681680	0.001142615	-1.235611074	-0.983610349
chr4	140221940	140223280	0.001142559	-1.221916145	-1.061781908
chr1	32644460	32646120	0.001142229	-1.237492556	-1.087496615
chr12	61485420	61485960	0.001141987	-1.170675557	-1.107306593
chr14	54790200	54790700	-0.001141833	-1.036590322	-1.320808643
chr3	157305860	157306280	-0.00114176	-0.831238432	-1.204942446
chr1	101004620	101005900	-0.001141669	-0.993153381	-1.044981587
chr11	18752500	18753000	-0.001141517	-0.961537336	-1.192911976
chr20	33543400	33543900	0.001141391	-1.219379966	-0.99748424
chr16	72042120	72043120	0.001141379	-1.178841917	-0.999855075
chr15	67238960	67239480	-0.001141216	-0.91957505	-1.03915644
chr7	73105380	73106640	0.001141133	-1.274023953	-1.121380508
chr11	64889020	64890200	0.001141118	-1.29617486	-1.08761099
chr5	156209020	156209400	-0.001141076	-1.036171464	-1.291133091
chr11	37766520	37766980	-0.001141055	-0.974494899	-1.233706905
chr4	106422400	106422880	-0.001140858	-0.966056867	-1.26074684
chr19	32237920	32239020	0.001140848	-1.040760554	-0.983505996
chr4	88565600	88566500	-0.001140812	-0.971844364	-1.214576379
chr19	31474520	31475100	-0.001140791	-1.035429283	-1.282255786
chr3	164783040	164783500	-0.001140521	-1.078169131	-1.2479711878
chr8	103062680	103063340	-0.00114035	-1.098909839	-1.351601297
chr1	231493620	231493880	-0.001140334	-0.98517739	-1.068557478
chr9	24781380	24781880	-0.001140227	-0.776320105	-0.900631848
chr19	18716720	18718260	-0.001140097	-0.906232641	-1.11638837
chr19	18716720	18718260	-0.001140097	-0.906232641	-1.11638837
chr17	40830260	40830560	0.001139697	-1.160604825	-0.964857947
chr17	17175080	17175420	0.001139209	-1.051180074	-0.936696343
chr17	17175080	17175420	0.001139209	-1.051180074	-0.936696343
chr10	5562940	5563420	-0.001139207	-0.949123632	-1.154628063
chr11	7044320	7044980	-0.001138811	-1.039280559	-1.279936486
chr7	124130820	124131280	-0.001138746	-1.108262752	-1.277732753
chr8	95565260	95566100	0.001138682	-1.219106395	-1.022943145
chr1	97955680	97956200	-0.001138465	-0.93590336	-1.194983389
chr12	123937660	123937860	-0.00113838	-0.957883178	-1.095001399
chr2	78224000	78224500	-0.001138374	-0.975245582	-1.24014951
chr16	23607180	23608360	0.001138291	-0.965954945	-0.845272721
chr2	161405320	161405760	-0.001138166	-0.950419834	-1.156582055
chr17	80407720	80408920	0.001138067	-1.134415215	-0.975359496
chr5	39246960	39247340	0.001138024	-1.247408866	-1.118613665
chr6	126216960	126217380	-0.001137896	-0.944552842	-1.142391215
chr2	70815480	70815960	-0.001137791	-0.971748768	-1.255843372
chr7	69469200	69469580	-0.001137726	-0.9965554093	-1.216783366
chr9	140116360	140116940	0.001137629	-1.178997363	-1.014464114
chr4	19502880	19503220	-0.001137579	-0.972754329	-1.15144365
chr2	108687880	108688340	-0.001137503	-0.886677846	-1.116739902
chr6	24719580	24721740	0.001137373	-1.329523014	-1.122641954
chr4	115654640	115655300	-0.001137332	-1.023237852	-1.181445731
chr7	15200980	15201500	0.00113726	-1.020399351	-1.030941367
chr8	88144720	88145180	-0.001136728	-0.860043047	-1.164175012
chr8	35445320	35445740	-0.001136429	-0.966708666	-1.181195106
chr4	180599960	180600820	0.001136428	-1.264461892	-1.123760265
chr3	83965500	83966400	-0.001136405	-0.975170772	-1.256957258
chr5	15096620	15096820	0.001136293	-1.311295098	-1.135702128
chr5	15096620	15096820	0.001136293	-1.311295098	-1.135702128
chr4	86396380	86397380	0.001136018	-1.306353373	-1.119241079
chr4	92920440	92920840	-0.001135704	-1.016483318	-1.223449845
chr3	191641820	191642300	-0.001135698	-0.959005572	-1.120434716
chr3	156855280	156855560	0.001135634	-1.112213549	-0.970979607
chr8	100509160	100509840	-0.001135509	-1.13363627	-1.353619757
chr3	144344520	144345000	-0.001135415	-0.926451006	-1.106674744
chr5	1651440	1652160	-0.001135342	-1.172678182	-1.226548804
chr3	13133360	13134260	0.001135294	-1.283927143	-1.129549081
chr3	13133340	13134280	0.001135294	-1.283927143	-1.129549081

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr9	77392040	77392280	0.001135176	-0.979112407	-0.742126813
chr1	90541440	90541800	-0.001134799	-0.873516057	-1.076155547
chr15	50646380	50647820	0.001134656	-1.020069345	-0.825723727
chr6	114180080	114180400	0.001134613	-1.399820903	-1.234756282
chr12	109535160	109536580	0.001134564	-1.35404279	-1.185623256
chr19	56631580	56633420	0.001134498	-1.203354235	-1.101927637
chr1	201099940	201100500	-0.001134496	-0.961620831	-1.224764301
chr11	29481440	29482020	0.001134462	-1.256926898	-1.136622933
chr11	29481400	29482060	0.001134462	-1.256926898	-1.136622933
chr13	65637600	65638380	0.001134392	-1.427887725	-1.245241542
chr14	85558780	85559220	-0.001134371	-1.040248671	-1.235539049
chr6	16128900	16130160	0.001134291	-1.235075535	-0.998159502
chr13	63316480	63317060	-0.001133969	-1.14213951	-1.357935551
chr6	29972980	29974020	-0.001133963	-0.88812365	-0.969309645
chr1	229763720	229764040	-0.001133925	-1.047537926	-1.25463225
chr19	49121880	49123220	0.001133818	-1.308444168	-1.118023919
chr1	245206000	245206300	0.001133696	-1.277422257	-1.09044818
chr12	54718420	54719040	0.001133561	-1.419043888	-1.264571542
chr8	77401640	77402100	-0.001133247	-0.933537813	-1.189754947
chr9	91650660	91650940	-0.001132976	-0.789505842	-0.941251888
chr15	85196640	85198720	0.001132793	-1.114346531	-0.887929971
chr1	97956480	97956960	0.001132628	-1.194546859	-1.158963043
chr7	100381380	100381640	0.001132552	-1.10992712	-0.921840432
chr19	49588200	49589120	0.001132524	-1.128891559	-1.038462198
chr21	19605080	19605480	-0.001132358	-0.926850289	-1.102055958
chr2	187102220	187102780	-0.001132213	-1.110573007	-1.320226397
chr2	187102200	187102800	-0.001132213	-1.110573007	-1.320226397
chr5	174477600	174478300	-0.001132129	-1.041642898	-1.290815934
chr16	26911120	26912160	-0.001131767	-0.839262886	-0.973684583
chr1	69124700	69125220	-0.001131727	-0.951958155	-1.210801054
chr20	32580780	32582460	-0.001131685	-1.043499776	-1.100010994
chr19	4400080	4400860	0.001131635	-1.203576894	-1.039568734
chr11	33294160	33294600	0.001131487	-1.357886136	-1.1669939
chr16	65746500	65746900	-0.001131469	-0.918331872	-1.107158579
chr12	106129120	106129500	-0.001131124	-1.084334693	-1.207842955
chr12	106129100	106129520	-0.001131124	-1.084334693	-1.207842955
chr10	36017820	36018380	-0.001131054	-1.022276408	-1.289904546
chr2	26256440	26257360	0.001130928	-1.375107758	-1.195286368
chr2	162493360	162493780	0.001130799	-1.2055101	-1.079878731
chr21	45826640	45827320	0.001130798	-0.982912739	-0.842889837
chr6	64755580	64756220	-0.001130536	-1.064343084	-1.33129667
chr12	84653940	84654420	-0.001130487	-1.041948056	-1.299603064
chr18	52603120	52603780	-0.001130431	-1.116600604	-1.415878175
chr19	2189780	2190060	0.001130251	-1.048554456	-0.799100618
chr12	20285140	20285600	-0.00113018	-1.004129911	-1.235126711
chr19	3990200	3990520	0.001130116	-1.148484323	-0.951790286
chr19	3990200	3990520	0.001130116	-1.148484323	-0.951790286
chr12	56709540	56710800	0.001130108	-1.153849535	-1.012015065
chr20	5595660	5596060	0.001129569	-1.152239028	-1.034978512
chr1	66597060	66597460	-0.001129219	-0.917447877	-1.166034845
chr5	472240	473960	-0.001129087	-1.075290863	-1.141967456
chr2	204501160	204501540	-0.001128942	-0.975684563	-1.164734583
chr11	6675940	6677460	0.001128689	-1.326973437	-1.148867195
chr2	23123160	23123880	-0.001128497	-0.934205448	-1.174256504
chr18	42994520	42994920	-0.001128485	-1.101097498	-1.287193263
chr1	243911740	243912660	0.001128436	-1.124392772	-0.997174799
chr3	100309180	100310600	0.001128352	-1.294734666	-1.010365893
chr13	62236540	62237260	-0.001128226	-1.043470071	-1.217184028
chr5	18929820	18930260	-0.001127978	-0.839520793	-1.055777967
chr21	34960360	34961500	0.001127974	-1.085764994	-0.848697908
chr2	64506640	64507000	-0.001127947	-1.081725564	-1.207333137
chr2	64506560	64507080	-0.001127947	-1.081725564	-1.207333137
chr4	71381800	71382360	-0.001127866	-1.183401538	-1.372196705
chr19	29687380	29688000	-0.001127725	-0.931260045	-1.203890773
chr11	30340300	30341060	-0.001127677	-1.103901593	-1.337669185
chr1	239567840	239568260	-0.001127371	-1.064845959	-1.169035577
chr8	42126800	42127300	-0.001127365	-1.152372883	-1.284789458
chr5	173596520	173597100	-0.00112701	-1.005413784	-1.279390155
chr1	16623160	16623620	-0.001126853	-0.965628285	-1.105348608
chr15	41522520	41524080	0.001126646	-1.223560492	-1.008101958
chr20	8497160	8497500	-0.00112664	-1.094770177	-1.296144999
chr20	42274140	42274340	0.001126413	-1.315524646	-1.162828637

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr20	42274140	42274340	0.001126413	-1.315524646	-1.162828637
chr1	217657740	217658260	0.001125802	-1.173666385	-1.104115239
chr3	153051400	153052160	-0.001125438	-0.99451193	-1.208137389
chr3	83965460	83966380	-0.001125365	-1.002177203	-1.273529113
chr6	92065560	92066200	-0.00112525	-1.032058478	-1.253813343
chr1	36869640	36869920	-0.001124906	-0.866356642	-1.106734375
chr5	67558020	67558540	-0.00112471	-1.072569993	-1.198287286
chr4	180599980	180608020	0.001124549	-1.228493608	-1.095170229
chr3	196438660	196439660	0.001124377	-1.410483211	-1.22348077
chr11	535020	536200	0.001124199	-1.394803128	-1.229342641
chr7	107055900	107056960	0.00112409	-1.088646505	-0.938961414
chr2	117801200	117802720	0.001123844	-1.233730088	-1.185205102
chr20	8141580	8142060	0.001123814	-0.970030219	-0.977849271
chr19	48770300	48770600	0.001123463	-1.135730546	-1.006824031
chr4	129432820	129433300	-0.001123462	-1.161003896	-1.29064776
chr1	102559220	102559800	-0.001123384	-1.11370035	-1.177607611
chr4	21347300	21348140	-0.001122937	-1.02068659	-1.192800604
chr8	145687440	145688840	-0.00112291	-1.175756771	-1.228881145
chr2	4158380	4158900	0.001122898	-1.332918825	-1.128579419
chr2	4158380	4158900	0.001122898	-1.332918825	-1.128579419
chr10	3901900	3902260	-0.001122748	-1.042569049	-1.250764133
chr9	130632220	130632500	0.001122689	-1.094774663	-0.873974171
chr2	10219600	10220920	0.001122665	-1.179083573	-1.035567809
chr7	122637900	122638440	-0.001122655	-0.886989278	-1.196361455
chr6	148764420	148764760	-0.001122607	-1.038831046	-1.224342262
chr6	22481600	22482120	-0.001122238	-0.885240307	-1.209091425
chr4	172376420	172376620	0.001122237	-1.426327096	-1.268411574
chr9	33264020	33265920	0.0011222	-1.173668256	-1.037777493
chr19	31839740	31842060	0.001121394	-1.172644063	-0.969488876
chr19	58919740	58920140	0.001121206	-1.268373501	-1.102997442
chr11	45168040	45169320	0.001121116	-1.350107732	-1.165279993
chr22	38239380	38240680	0.001121012	-1.044212692	-0.851669495
chr8	88914080	88914680	-0.00112101	-1.117759011	-1.328287316
chr19	40696760	40698420	0.001120971	-1.194777212	-0.970914781
chr21	35445100	35446600	-0.001120914	-1.08052349	-1.180491364
chr19	46520040	46520380	0.001120854	-1.289323129	-1.137254443
chr3	50337740	50337940	-0.001120559	-0.828507476	-0.945247469
chr19	2950540	2951280	0.001120494	-1.075599092	-0.946001874
chr14	99247220	99247920	-0.001120115	-1.033460546	-1.285129205
chr1	231015140	231015960	0.001120044	-1.201718553	-0.885925716
chr3	89059260	89059740	-0.001119815	-1.100841778	-1.202583128
chr7	36797240	36797900	-0.001119331	-1.065118594	-1.305357555
chr7	5405700	5405960	-0.00111932	-0.960656086	-1.058456147
chr17	43393900	43395480	0.001119296	-1.177521408	-1.036676354
chr4	155651900	155652280	-0.001119259	-0.775520003	-1.067081554
chr4	177241880	177245000	0.001119171	-1.342779907	-1.149136899
chr19	33571920	33572240	0.001119029	-1.241294754	-1.067876961
chr10	34955580	34955820	-0.001118756	-0.831937311	-0.987734967
chr8	145132760	145134020	0.001118737	-1.277098199	-1.110055454
chr19	42103640	42104560	0.001118399	-1.151407518	-0.971630291
chr14	92320580	92321020	0.001118308	-1.184014416	-0.956207613
chr19	5084160	5084860	-0.001118278	-1.059710319	-1.298218786
chr6	67142980	67144460	0.001118267	-1.274435382	-1.031651884
chr15	76109940	76110320	0.001118142	-0.912242945	-0.846722625
chr6	33289820	33291160	0.001118023	-1.056676032	-0.909268063
chr19	56110320	56112400	0.001117962	-1.023340817	-0.988172521
chr8	76301960	76302440	-0.001117917	-1.007777762	-1.242820893
chr1	228369840	228370680	0.001117752	-1.225032704	-1.106815887
chr8	137838340	137838900	-0.001117541	-1.092193816	-1.29642051
chr10	111767280	111768520	-0.001117293	-0.786626739	-0.877342738
chr20	60941620	60943020	-0.001117245	-0.913677156	-0.987785148
chr16	84481040	84481700	-0.001117133	-0.958864366	-1.197615923
chr15	96103540	96104020	0.001117001	-1.042403779	-1.016709208
chr6	79263300	79264120	-0.001116893	-1.084551423	-1.282262551
chr19	16738280	16739880	0.001116883	-1.283490539	-1.161702176
chr13	83752300	83752800	-0.001116802	-0.982574501	-1.150677658
chr12	17439480	17439900	-0.001116519	-1.004948823	-1.267973689
chr14	24610640	24611120	0.001116455	-1.299304629	-1.17497304
chr14	24610620	24611140	0.001116455	-1.299304629	-1.17497304
chr19	41076060	41077360	0.00111641	-1.180481949	-1.060701466
chr1	152452400	152452860	-0.001116347	-1.075847208	-1.196734636
chr1	152452380	152452880	-0.001116347	-1.075847208	-1.196734636

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr2	124074060	124074660	-0.001116339	-1.067357276	-1.271746145
chr11	69191700	69192420	0.001115972	-1.131786822	-1.007487428
chr21	35770040	35770500	-0.001115937	-0.964110681	-1.064844399
chr14	27162300	27162980	-0.001115893	-1.070561085	-1.176495445
chr2	226618300	226618740	0.00111587	-0.931024566	-1.189451748
chr2	226618280	226618760	-0.00111587	-0.931024566	-1.189451748
chr14	85364120	85364580	-0.001115834	-1.175280367	-1.326095968
chr16	27199700	27200340	0.001115761	-1.260707376	-1.116895942
chr18	29443820	29444200	-0.001115705	-0.926894587	-1.184438149
chr3	167443340	167443820	-0.001115384	-1.121556921	-1.23329988
chr14	76415500	76415960	0.001115382	-1.133198006	-1.090222245
chr1	60762080	60762500	-0.001115358	-0.982789554	-1.116177628
chr2	2113500	2113920	-0.001114995	-1.019835229	-1.134846458
chr16	89783220	89783700	-0.001114951	-0.999204351	-1.11888071
chr21	25248920	25249240	-0.001114911	-0.802651704	-0.956548276
chr10	102672140	102673320	0.001114825	-1.19200308	-1.006318755
chr3	183068780	183069240	0.001114713	-1.221137217	-1.140934269
chr8	3380840	3382380	0.001114553	-1.184901933	-1.014544373
chr12	15397620	15398140	0.00111455	-1.30934827	-1.156424928
chr9	29913660	29914220	-0.001114521	-0.816202868	-1.085463902
chr21	46256260	46256540	-0.001114516	-0.917816936	-0.925514626
chr5	28966980	28967660	-0.001114145	-1.048729	-1.295236978
chr19	41283340	41284980	0.001113898	-1.10285478	-0.952502089
chr14	55030800	55031020	0.0011136	-1.156533503	-1.049368055
chr14	55737260	55738740	0.001113468	-1.33420851	-1.040059857
chr2	46847720	46847980	-0.00111319	-0.863555477	-1.056419343
chr2	46847660	46848040	-0.00111319	-0.863555477	-1.056419343
chr3	13983660	13984040	-0.001113138	-0.830867367	-1.185744431
chr2	193765260	193765900	-0.001113119	-1.078239583	-1.327371432
chr4	27050000	27050300	0.00111294	-1.209494807	-1.05380676
chr1	32014200	32015120	0.001112905	-1.252102869	-1.014673637
chr20	57617280	57618520	0.001112624	-1.303587265	-1.144255648
chr5	161111580	161112100	-0.001112329	-1.100409392	-1.319142569
chr2	99224460	99225660	0.001112213	-1.369638572	-1.157429396
chr4	127533920	127534460	-0.001112	-1.129557742	-1.303446464
chr4	108910520	108911480	0.001111941	-1.174085499	-0.941813424
chr6	48552000	48552380	-0.001111881	-0.853231275	-1.203657782
chr1	90800040	90800980	-0.00111188	-1.067844192	-1.307120189
chr11	90458960	90459360	-0.001111741	-0.914072172	-1.12725033
chr5	167218120	167218760	-0.001111722	-1.127266981	-1.329005372
chr17	80967640	80968180	0.001111385	-1.198388215	-1.020425933
chr21	20526120	20526520	-0.00111119	-0.846278415	-0.999212391
chr21	20526080	20526560	-0.00111119	-0.846278415	-0.999212391
chr2	137188660	137189220	-0.001111118	-1.011205108	-1.210302551
chr13	55876980	55877340	-0.001111035	-1.028383806	-1.213789354
chr7	30174080	30175340	0.001111001	-1.169601408	-1.032121283
chr11	65097440	65097700	0.00111079	-1.278904405	-1.13729655
chr3	38203780	38204040	-0.001110736	-1.043187181	-1.267779153
chr3	38203780	38204040	-0.001110736	-1.043187181	-1.267779153
chr8	126009800	126011200	0.001110577	-1.225607156	-1.029513898
chr17	65713100	65714480	0.001110433	-1.060762879	-0.849793157
chr7	148292140	148293020	-0.001110241	-1.110868635	-1.38000018
chr9	19432380	19432940	-0.001109838	-0.906777604	-1.047021544
chr1	204463320	204464320	0.001109662	-1.160275821	-0.962974817
chr12	60278380	60279160	-0.001109632	-1.145182368	-1.371858177
chr3	131519980	131520600	-0.001109233	-1.065702335	-1.253109212
chr4	171895040	171895320	-0.001109221	-1.188100726	-1.329545183
chr4	171895040	171895320	-0.001109221	-1.188100726	-1.329545183
chr7	150948700	150949240	0.00110916	-1.176275801	-1.000721177
chr3	187471920	187472320	-0.001109075	-1.010081127	-1.201979465
chr9	107255100	107255360	-0.001108693	-0.788941911	-0.996220795
chr19	45251560	45252340	0.001108604	-1.125192241	-0.957077582
chr10	102858380	102858880	0.001108592	-1.326574452	-1.231909776
chr20	32617120	32617480	-0.001108515	-0.96447458	-1.099950838
chr3	175940780	175941100	-0.001108397	-1.021356737	-1.153948644
chr13	101732600	101733320	-0.001108267	-1.065862241	-1.371189059
chr13	101732580	101733440	-0.001108267	-1.065862241	-1.371189059
chr8	113795400	113795920	0.001108178	-1.287508235	-1.041498426
chr14	32545760	32546960	0.001108123	-1.331727282	-1.104769089
chr14	32545580	32547140	0.001108123	-1.331727282	-1.104769089
chr7	2749360	2749660	0.00110797	-1.099791669	-0.963744313
chr2	180128620	180129840	0.001107824	-1.359182984	-1.1439275

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr10	103744760	103745380	-0.001107812	-1.085420594	-1.271328849
chr5	146776200	146776900	-0.001107667	-1.012483053	-1.236119827
chr5	146776200	146776900	-0.001107667	-1.012483053	-1.236119827
chr4	88574320	88574820	-0.001107463	-1.155274433	-1.287118148
chr13	100612600	100613100	-0.001107232	-1.030237645	-1.245534107
chr19	55999420	55999600	0.00110723	-1.164295262	-1.032694178
chr13	98223520	98224420	0.001107111	-1.218091689	-1.132991922
chr8	28930380	28930820	0.001107104	-1.163634311	-1.002917542
chr17	43091540	43091880	-0.001107086	-1.066531017	-1.268892329
chr21	18884680	18885820	0.001107086	-0.911982507	-0.642185424
chr4	71570200	71571620	0.001106177	-1.179700166	-0.961242605
chr15	75164820	75166040	0.001105956	-1.197027278	-1.043164783
chr15	42499580	42501460	0.001105943	-1.119390287	-1.023250186
chr4	172377520	172379560	0.00110585	-1.413560809	-1.289344738
chr9	77995640	77995980	-0.001105782	-0.859771582	-1.058143293
chr17	47646760	47647080	0.001105742	-1.179704185	-1.020616566
chr5	149339380	149341000	0.001105696	-1.329290316	-1.1052653
chr19	918620	919120	0.001105665	-1.193126015	-0.988711704
chr12	80946180	80946680	0.001105542	-1.248979071	-1.118391957
chr16	4012880	4013320	0.001105481	-0.986897932	-0.913261925
chr6	104834880	104835600	-0.00110538	-1.148770254	-1.361949852
chr16	76341200	76341640	-0.001105313	-0.860072583	-1.03761654
chr14	54790180	54790700	-0.001105228	-1.014925905	-1.273216775
chr12	58005400	58005920	0.001105225	-1.274916687	-1.083672963
chr7	28543080	28543500	0.00110518	-1.08692176	-0.856566125
chr5	180162560	180163140	-0.001105065	-0.930764908	-1.192195198
chr6	155054220	155055540	0.001104816	-1.194462809	-1.008763291
chr7	80477100	80478540	0.001104658	-1.282374857	-1.148826953
chr11	66623620	66625040	-0.001104626	-0.997960155	-1.049134801
chr4	1080160	1081500	0.001104473	-1.322799963	-1.093214382
chr12	106695600	106697480	0.001104437	-1.285150932	-1.048520032
chr5	67558880	67559280	-0.001104418	-0.974748799	-1.08187751
chr5	67558880	67559280	-0.001104418	-0.974748799	-1.08187751
chr3	80713280	80713800	-0.001103741	-1.113039043	-1.368171391
chr2	3605340	3606680	0.001103586	-1.370873561	-1.122037621
chr3	140949980	140951400	-0.001103438	-1.159002703	-1.208638239
chr11	62554000	62555160	0.001103415	-1.191797991	-1.075183772
chr11	46382920	46383180	0.001103177	-1.1893118	-0.991511254
chr2	85197640	85199320	0.001102977	-1.273278124	-1.112673488
chr1	150336020	150337300	0.001102852	-1.085425464	-0.947321156
chr6	126216900	126217400	-0.001102692	-0.949887483	-1.136352635
chr20	43948200	43948500	0.001102689	-1.239445031	-1.005015613
chr11	2400340	2400800	0.001102652	-1.399573295	-1.177097548
chr16	28099980	28101420	0.001102207	-1.072212805	-0.881094079
chr22	37623540	37624000	0.001102157	-1.0421623	-0.867519228
chr5	105900100	105900780	-0.001102124	-1.083621017	-1.260232218
chr3	154851260	154851780	-0.001102118	-1.054997965	-1.193860898
chr1	40254040	40255180	0.001101727	-1.253137358	-1.08225816
chr3	54769880	54770360	-0.001101714	-1.095202633	-1.290807407
chr3	23335900	23336500	-0.001101337	-0.979964724	-1.289308281
chr1	169323640	169324200	-0.001101321	-0.947386528	-1.091804501
chr9	28470640	28471160	-0.001101059	-0.726924312	-1.009727056
chr20	23342280	23343500	0.001100957	-1.356818021	-1.172992329
chr2	198575320	198575820	-0.001100952	-0.718785184	-1.050527239
chr7	74235520	74237280	0.001100693	-1.230262266	-1.019993099
chr21	45410820	45411060	-0.001100684	-0.792276369	-0.965143807
chr21	45410820	45411060	-0.001100684	-0.792276369	-0.965143807
chr15	84343200	84343780	0.001100151	-1.094850715	-1.084557239
chr22	27131840	27132880	-0.001100052	-0.797451886	-0.972393274
chr22	27131820	27132900	-0.001100052	-0.797451886	-0.972393274
chr5	158639520	158639920	-0.0011099874	-1.010582153	-1.216650835
chr16	54180400	54180760	-0.0011099667	-0.807984262	-1.128075658
chr4	163470660	163471100	-0.0011099603	-0.993675793	-1.060225907
chr4	163470620	163471140	-0.0011099603	-0.993675793	-1.060225907
chr8	97742940	97743320	0.0011099399	-1.162384109	-0.956382864
chr7	89697620	89698040	0.0011099327	-1.097587384	-1.071577078
chr7	89697580	89698080	0.0011099327	-1.097587384	-1.071577078
chr6	147523520	147523900	0.0011099054	-1.357609421	-1.153512978
chr6	125465720	125466180	-0.0011098988	-1.165933018	-1.366378828
chr22	24407240	24408240	0.0011098737	-1.047785904	-0.893603964
chr7	57183580	57184880	0.0011098567	-1.202976747	-1.04662245
chr8	86868800	86869500	-0.0011098248	-0.999644117	-1.207265331

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr19	56594960	56595380	0.001098019	-1.165147244	-1.103724531
chr19	56594940	56595400	0.001098019	-1.165147244	-1.103724531
chr7	111738420	111738920	-0.001097921	-0.826923421	-1.103707589
chr1	95699180	95700400	0.001097621	-1.149401607	-0.944441514
chr7	148755200	148755500	-0.001097488	-0.880013089	-1.096136148
chr7	148755160	148755620	-0.001097488	-0.880013089	-1.096136148
chr4	33693140	33693540	-0.001097471	-0.865137637	-1.044955392
chr19	3134060	3134420	0.001097417	-1.144341277	-1.037608229
chr9	117493200	117493680	0.001097371	-1.151888295	-0.934357278
chr9	33264260	33265600	0.001097052	-1.189286187	-1.036962144
chr4	177005700	177006180	-0.001097042	-0.9330834	-1.197246707
chr13	104688320	104688920	-0.001097009	-0.895616496	-1.077176686
chr10	30702980	30704440	-0.001096979	-0.918247112	-1.215735334
chr19	57791180	57792280	0.001096317	-1.116616158	-0.982731292
chr1	156906060	156906500	-0.001096258	-1.107613253	-1.233349572
chr8	79385240	79385780	-0.001096241	-0.782338081	-1.038704805
chr7	50571980	50572500	0.001096197	-1.102394373	-1.040023417
chr19	10023860	10025700	0.001096082	-1.017057898	-0.851433151
chr11	38971200	38971740	-0.001096043	-1.193209348	-1.315427705
chr21	48081540	48082200	0.001096021	-1.188069531	-1.060079015
chr10	74123880	74124520	0.001095907	-1.196371136	-1.004279083
chr5	62838940	62839380	-0.001095898	-0.996690402	-1.20226593
chr12	122471900	122472300	-0.001095878	-1.095755515	-1.180200784
chr2	111435360	111436240	0.001095734	-1.306648796	-1.089836851
chr14	64280940	64281380	-0.001095723	-1.052770315	-1.259899842
chr10	93169340	93170900	-0.001095696	-1.183676112	-1.257490586
chr8	106226580	106227200	-0.001095579	-0.998208783	-1.258040604
chr22	48503440	48504300	-0.001095499	-0.842729841	-1.088430367
chr7	3386180	3386680	0.001095364	-1.117001369	-1.033633415
chr2	77683860	77684400	-0.001095151	-0.980148032	-1.219285231
chr20	55921500	55921780	0.001094637	-1.199103232	-0.982504957
chr6	30512500	30512760	0.001094599	-1.277684009	-1.017752192
chr10	62060680	62061180	-0.001094445	-0.921909654	-1.121344318
chr18	9474780	9476080	0.00109429	-1.393981088	-1.202955433
chr5	131028660	131029220	0.001094068	-1.272436106	-1.126649192
chr9	130533240	130534160	-0.00109376	-0.943225458	-1.026449294
chr20	10282300	10282740	-0.001093575	-1.050034265	-1.323189808
chr5	67045300	67045980	-0.001093574	-0.89430094	-1.092175864
chr3	166425180	166425580	-0.001093367	-0.964526762	-1.089029838
chr3	166425160	166425600	-0.001093367	-0.964526762	-1.089029838
chr2	41307060	41307560	-0.001093192	-0.9096711379	-1.186745892
chr11	97716180	97716680	0.001093177	-1.144286241	-1.143598928
chr6	111579900	111581120	0.001093171	-1.382949313	-1.187148683
chr2	180737200	180737580	0.001093025	-1.244250984	-1.094186565
chr16	11679900	11681240	0.001092484	-1.160749397	-0.892544027
chr16	4321800	4322300	0.001092378	-1.075430045	-0.880071276
chr19	13213460	13213880	0.001092025	-1.147840876	-0.932274767
chr2	47482920	47483460	-0.001092018	-1.009927199	-1.243062235
chr11	57143540	57144180	0.00109195	-1.263768564	-0.998729933
chr5	108265880	108266500	-0.001091944	-1.178237488	-1.259500336
chr5	40649620	40651400	0.001091915	-1.246592501	-1.024580214
chr6	25206440	25207300	0.001091743	-1.347147337	-1.241971103
chr20	48785940	48786220	0.001091691	-1.331968932	-1.165253538
chr5	26793020	26794260	-0.001091617	-1.172252717	-1.371655031
chr10	78386740	78387280	-0.001091606	-1.143229332	-1.260482582
chr11	65097420	65097700	0.001091543	-1.261145394	-1.123884619
chr3	101625560	101626360	0.001091447	-1.185539583	-1.017533128
chr7	6565820	6566700	0.001091413	-1.174796013	-0.938375745
chr6	50699300	50699580	0.001091292	-1.108813454	-0.898498286
chr2	52382440	52382820	-0.001091135	-0.871756956	-1.111138895
chr6	152345560	152346160	-0.00109113	-1.061589304	-1.219961692
chr9	110877680	110878320	-0.001091126	-0.955019969	-1.201101392
chr20	35374080	35374780	0.001091076	-1.24962973	-1.094375442
chr9	11474040	11474500	-0.001091071	-0.619300316	-0.840528515
chr21	30160360	30160680	-0.001091053	-0.832952112	-1.083452822
chr21	30160360	30160680	-0.001091053	-0.832952112	-1.083452822
chr18	65661240	65661640	-0.001090935	-1.111679364	-1.339489902
chr16	57713380	57714500	-0.001090639	-0.876149696	-0.990918627
chr7	4099080	4099680	-0.001090536	-1.001857562	-1.14591404
chr11	71791120	71792520	0.001090346	-1.362064533	-1.191380275
chr2	77683900	77684320	-0.001090293	-0.937454227	-1.179498658
chr9	103593940	103594260	0.001090214	-0.974978529	-0.957714593

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr4	12795580	12796660	-0.001090206	-1.019977757	-1.180906224
chr17	74931680	74932240	-0.001090016	-1.049052857	-1.280155807
chr8	70173320	70173740	-0.001089965	-1.082218406	-1.25877137
chr6	159429680	159429920	0.001089755	-1.117883278	-0.942911914
chr2	21370140	21370520	-0.001089559	-0.946711317	-1.161338823
chr2	21370080	21370580	-0.001089559	-0.946711317	-1.161338823
chr12	21122900	21123460	-0.001089421	-0.983488598	-1.26567191
chr7	35879540	35879980	-0.001089057	-0.97710005	-1.10700535
chr2	186867040	186867540	-0.001088855	-0.854030232	-1.054433747
chr2	61900300	61900760	-0.001088855	-1.028951469	-1.209383461
chr2	61900300	61900760	-0.001088855	-1.028951469	-1.209383461
chr6	9777940	9778660	0.001088589	-1.049101968	-1.052998008
chr14	86290520	86290920	-0.001088568	-0.951366952	-1.210529378
chr19	48672780	48674520	0.001088556	-1.291425723	-1.129446179
chr1	203008500	203008760	0.001088448	-1.193390262	-1.009547415
chr21	40751580	40752840	0.001088434	-1.104389244	-0.943329724
chr16	9358600	9359020	0.001088145	-1.239415843	-1.136710051
chr9	130747820	130748180	-0.001088099	-0.932356577	-1.069537787
chr9	6930300	6930920	-0.001088089	-0.842753247	-1.133149393
chr5	26882960	26883420	-0.001088071	-1.081484022	-1.249026938
chr16	54646980	54647700	-0.001087959	-0.755494408	-1.073637836
chr8	76163520	76164180	0.001087914	-1.316302402	-1.246208936
chr7	4721560	4722840	0.001087844	-1.311288871	-1.054803664
chr11	69177440	69178640	0.001087801	-1.329029567	-1.252189201
chr10	30702980	30704220	-0.001087709	-0.920711138	-1.155284202
chr11	59962720	59963280	-0.001087708	-1.084098737	-1.333081606
chr4	151096220	151096580	-0.00108765	-0.973051645	-1.145733493
chr17	54990900	54991900	0.001087472	-1.077709902	-0.933148836
chr2	195033040	195033560	-0.001087231	-1.052065488	-1.300784911
chr1	200456720	200457140	0.001087135	-1.151795933	-0.985817069
chr11	13428180	13428460	-0.001087083	-0.695226343	-0.914646217
chr17	75301820	75302340	-0.00108699	-0.924115612	-1.051372544
chr17	617500	618620	0.001086786	-1.130163325	-0.924921129
chr4	31338280	31338880	0.001086682	-1.36449743	-1.264994252
chr19	39902480	39903660	0.001086566	-1.195637078	-1.022827429
chr19	39902480	39903660	0.001086566	-1.195637078	-1.022827429
chr6	52149340	52150000	0.001086476	-1.26766284	-1.004076996
chr4	110132180	110132700	-0.001086464	-1.138841769	-1.331830486
chr7	107365640	107365900	0.001086464	-1.012598736	-0.871277019
chr4	66440040	66440680	-0.001086375	-1.045819546	-1.308331721
chr6	30687820	30689700	0.001086324	-1.201706216	-1.014122001
chr2	97559940	97560820	-0.001086285	-1.177050644	-1.223466985
chr15	59396620	59397920	0.001086248	-1.115879175	-0.93755101
chr11	47950860	47951560	-0.001086148	-1.19312658	-1.378975663
chr13	91960820	91961420	-0.001086113	-1.175733858	-1.333323847
chr4	177240460	177241900	0.001085891	-1.358104108	-1.191522454
chr16	68056960	68057380	0.001085785	-1.277916694	-1.090985884
chr21	18457280	18457780	0.001085706	-1.145080666	-1.025117018
chr21	18457280	18457780	0.001085706	-1.145080666	-1.025117018
chr20	48428740	48430060	0.001085699	-1.239621471	-0.991289923
chr5	25257920	25258320	-0.001085404	-0.941933463	-1.191757354
chr14	71702040	71702500	-0.00108529	-1.06837264	-1.283937185
chr14	71702040	71702500	-0.00108529	-1.06837264	-1.283937185
chr15	61332120	61332580	-0.001085275	-0.94707246	-1.198116328
chr8	117496400	117496800	-0.001085113	-1.06069849	-1.263252543
chr9	29868280	29868800	-0.001084945	-0.912245924	-1.154374064
chr16	21036480	21037020	0.001084684	-1.240437358	-1.171655265
chr1	239567800	239568260	-0.001084609	-1.015917406	-1.180758439
chr14	95979960	95980320	-0.001084594	-1.015591952	-1.130026049
chr13	106018760	106019360	-0.001084511	-1.045106176	-1.316070496
chr13	106018740	106019380	-0.001084511	-1.045106176	-1.316070496
chr1	36590460	36591160	0.001084453	-1.138734614	-0.926862975
chr3	12933540	12934700	0.001084349	-1.424673647	-1.229486585
chr3	12933520	12934720	0.001084349	-1.424673647	-1.229486585
chr13	40479660	40480040	-0.001084332	-1.000230845	-1.158038231
chr2	148517700	148518200	-0.001084279	-1.158928725	-1.308702313
chr20	1630460	1630920	-0.001084267	-0.972196519	-1.157315592
chr12	9246740	9247180	-0.001084082	-1.010508681	-1.204558992
chr7	16684280	16686780	0.001083934	-1.261899363	-1.048029884
chr17	56640740	56641220	-0.001083676	-0.990746174	-1.103155557
chr8	42248640	42250180	0.00108362	-1.194967705	-1.075724318
chr1	215799320	215799960	0.001083569	-1.13347652	-0.963342446

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr19	5719700	5720900	0.001083034	-1.22493442	-1.112173442
chr6	99917160	99917540	-0.001082943	-0.991931711	-1.193051155
chr1	72209700	72210280	-0.001082904	-0.90094982	-1.173500667
chr4	31403380	31404040	-0.001082883	-1.10086198	-1.280549441
chr14	50697520	50699160	0.001082812	-1.201542342	-1.035111146
chr3	144344520	144344960	-0.001082675	-1.040066072	-1.214584111
chr7	38368080	38368580	-0.001082317	-1.057372202	-1.294187446
chr15	69754900	69755460	0.001082204	-1.244763015	-1.046679509
chr4	165676540	165676900	-0.001082168	-1.246323043	-1.35151528
chr9	74886840	74887140	0.001081757	-1.154021774	-0.922963744
chr6	79263420	79264120	-0.001081571	-1.073521395	-1.267507841
chr5	23597340	23597780	-0.001081564	-0.959265119	-1.189786331
chr8	23549880	23550780	0.001081403	-1.202319047	-1.033046182
chr4	93047220	93047640	-0.001081343	-0.871557241	-1.104076297
chr20	59928500	59928960	0.001080798	-1.18315954	-0.993317187
chr1	33721440	33722700	0.001080763	-1.242691513	-1.093058437
chr1	197144360	197144780	-0.001080757	-0.909456484	-1.090633947
chr2	102968660	102969120	-0.001080716	-1.218820791	-1.379238452
chr15	74753180	74754080	0.00108058	-1.245652291	-1.0899561
chr15	84347280	84347880	-0.001080538	-0.907233661	-1.226336505
chr19	40969280	40969660	-0.001080498	-0.955821473	-1.015675027
chr3	151478780	151479200	-0.001080426	-1.165490309	-1.320855829
chr1	147830900	147831220	-0.001080351	-1.061224256	-1.280212429
chr1	147830900	147831220	-0.001080351	-1.061224256	-1.280212429
chr4	186145480	186146020	-0.001080326	-1.198639956	-1.358394434
chr4	81122900	81125140	0.001080144	-1.293817655	-1.079769653
chr16	50099220	50101100	0.001080075	-1.010754521	-0.850087949
chr13	58506380	58506900	0.001080037	-1.351863529	-1.283092785
chr8	35646400	35646920	-0.001079917	-1.131315312	-1.282473847
chr3	158509140	158509420	0.001079803	-1.195370738	-0.949044602
chr11	2035840	2036240	-0.001079244	-1.066866339	-1.177756373
chr11	2035820	2036260	-0.001079244	-1.066866339	-1.177756373
chr7	29885720	29887080	0.001078951	-1.094353005	-0.893687438
chr3	4073140	4073360	-0.00107891	-1.116432483	-1.285169114
chr14	91867420	91867760	0.001078678	-1.288606733	-1.186163427
chr9	94185600	94187160	0.00107862	-1.169725633	-0.971245736
chr9	106171140	106171580	-0.00107857	-0.723609441	-1.005076883
chr6	40604380	40605000	-0.001078501	-1.238874938	-1.423049398
chr10	78398720	78399340	-0.001078198	-1.186595766	-1.334389869
chr2	195612000	195612400	-0.001078125	-0.806389814	-1.028394919
chr1	117959960	117960380	-0.001078115	-0.91729762	-1.163141634
chr1	40960180	40960680	0.001078026	-1.152912469	-1.106243345
chr2	84459120	84459700	-0.001078	-1.099961143	-1.298223503
chr16	82149060	82149540	-0.001077948	-0.732934058	-1.041386856
chr16	82149060	82149540	-0.001077948	-0.732934058	-1.041386856
chr10	101573660	101574600	0.001077648	-1.1916788	-1.028861027
chr19	14007040	14007680	0.001077495	-1.032599654	-0.977924358
chr12	81334760	81335300	-0.001077476	-0.978616934	-1.247633058
chr16	88819300	88819940	-0.001077439	-1.107692769	-1.225744556
chr2	163197560	163198020	-0.001077184	-1.007479553	-1.199894016
chr16	11690160	11690760	-0.001077164	-0.916069173	-0.988061817
chr11	3012980	3014180	0.001077146	-1.221445826	-1.067656126
chr7	29163020	29163460	-0.001077136	-0.931198914	-1.174397974
chr19	50528020	50529540	0.001077005	-1.242319446	-1.088896485
chr8	6350040	6350480	-0.001076898	-0.957041394	-1.15872325
chr2	102593960	102594460	-0.001076402	-1.141313388	-1.267769129
chr6	31734660	31735040	0.001076257	-1.286360503	-1.210203247
chr6	31734600	31735100	0.001076257	-1.286360503	-1.210203247
chr7	17942060	17943240	0.001075921	-1.299273369	-1.12763084
chr6	135989480	135990200	-0.001075774	-1.16586908	-1.355166773
chr5	126582280	126582860	-0.001075322	-1.094803334	-1.356181351
chr3	119641080	119641500	-0.001075297	-1.032733709	-1.279359395
chr14	102248240	102248540	-0.00107522	-1.161393245	-1.256975047
chr19	50676240	50676560	0.001075141	-1.061388134	-0.816153937
chr19	50676240	50676560	0.001075141	-1.061388134	-0.816153937
chr1	110025960	110027540	0.001074968	-1.049686735	-0.918270279
chr4	152690260	152690860	-0.001074942	-0.985186366	-1.180098605
chr2	219134740	219135620	0.001074744	-1.401773131	-1.172962585
chr3	55748440	55748980	-0.001074418	-1.087554017	-1.228678293
chr3	95740600	95741140	-0.001074171	-1.252988882	-1.398877526
chr11	125462260	125463180	0.001074055	-1.325602908	-1.213919689
chr16	30758880	30760660	0.001073868	-1.180113818	-0.931229794

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr15	84470160	84470660	-0.001073684	-0.996136368	-1.178800006
chr19	18043340	18044240	0.001073222	-1.249012506	-1.077929733
chr19	41304580	41305860	0.001072977	-1.122493246	-0.942796719
chr19	41304560	41305900	0.001072977	-1.122493246	-0.942796719
chr1	179956320	179956900	-0.001072826	-0.91859188	-1.197742184
chr4	85892560	85892820	0.001072801	-1.242412642	-0.981761846
chr10	123617920	123618340	-0.001072633	-1.000239366	-1.148501706
chr11	10955300	10955620	0.001072609	-1.26339542	-1.131005529
chr11	10955300	10955620	0.001072609	-1.26339542	-1.131005529
chr6	27763680	27763960	-0.001072333	-1.046884755	-1.150170129
chr2	222246580	222246920	-0.001071874	-1.057221584	-1.255963393
chr9	37485060	37486700	0.001071609	-1.100013475	-0.901000507
chr17	78866800	78867500	0.001071499	-1.161495437	-0.988537634
chr9	137299160	137300040	-0.001071479	-0.886572606	-0.992375213
chr22	48377280	48377740	-0.001071361	-0.884940862	-1.159891969
chr13	25874880	25876600	0.001071334	-1.320467827	-1.116968099
chr8	77477240	77477660	-0.001071148	-1.052401443	-1.235159457
chr10	43950820	43951440	0.001071118	-1.22334767	-1.072625184
chr11	127538480	127539040	-0.001071029	-1.141499427	-1.345315146
chr17	40828760	40829420	0.001070921	-1.11756298	-0.913943178
chr11	65651680	65652900	0.00107059	-1.332162327	-1.072456699
chr17	61689640	61689920	0.001070581	-1.189480905	-1.079107101
chr16	29973040	29973940	-0.001070569	-0.913083159	-0.985061516
chr18	29443800	29444240	-0.001070559	-0.925180144	-1.18684329
chr4	127572440	127572920	-0.001070403	-1.022117379	-1.20466167
chr8	78598560	78599020	-0.001070395	-1.160520366	-1.27915887
chr13	46731200	46731500	0.001070004	-1.163551199	-0.991231116
chr12	7348440	7349080	-0.001069869	-1.109491932	-1.334518168
chr1	10270200	10271460	0.001069739	-1.30706331	-1.110155677
chr9	140116340	140116940	0.001069703	-1.16128793	-1.014464114
chr6	145676380	145676980	-0.001069494	-1.032671415	-1.205769579
chr9	91550660	91551040	-0.001069343	-0.740921933	-0.965256916
chr12	131384320	131384780	-0.001069058	-1.038058239	-1.234661768
chr8	124002000	124002820	-0.001069016	-0.989419183	-1.249941196
chr20	16390420	16391140	-0.001068989	-0.998401428	-1.227355101
chr7	7513040	7513540	-0.001068899	-0.896293203	-1.131054629
chr22	42228740	42230040	0.001068519	-1.010291621	-0.822129629
chr5	24151400	24151920	-0.001068472	-1.090300811	-1.268814755
chr7	92485300	92485840	-0.001068407	-1.028620201	-1.214796373
chr19	12958120	12959020	0.001068094	-1.161456091	-1.00350827
chr5	19219880	19220520	-0.001068094	-1.063706416	-1.32330015
chr13	56317400	56318000	-0.001068081	-1.19610983	-1.39716488
chr5	141071200	141072440	0.001068081	-1.314697074	-1.069061508
chr12	8113300	8113620	0.001068025	-1.137035588	-1.014357338
chr21	47411140	47411540	0.001067421	-0.92463981	-0.758667893
chr15	75166780	75167220	0.001067315	-1.129674989	-1.006773293
chr14	44022060	44022480	0.001067255	-1.413207475	-1.295845023
chr1	166476500	166477040	-0.001067119	-0.905208659	-1.16300159
chr13	92031580	92032200	-0.001067109	-1.170640376	-1.314348922
chr4	26858780	26859820	0.001067069	-1.341157125	-1.159014698
chr9	115982920	115984240	0.001066943	-1.049368032	-0.937549885
chr17	3641020	3641320	0.001066931	-1.217200109	-1.010630052
chr5	92645780	92646220	-0.001066815	-0.915512364	-1.168415949
chr5	92645740	92646260	-0.001066815	-0.915512364	-1.168415949
chr7	2791760	27921120	-0.001066697	-1.064903666	-1.180061922
chr12	27295100	27295360	0.001066646	-1.200450851	-1.052592689
chr11	38195860	38196400	0.001066617	-1.158351559	-1.132538695
chr13	89925960	89926520	-0.001066543	-1.168112382	-1.336081471
chr11	28039860	28040220	-0.001066397	-0.992700451	-1.238555256
chr10	17313520	17313860	-0.001065984	-0.983547071	-1.172097644
chr19	10683080	10683320	0.001065894	-1.027905854	-0.889412828
chr19	10683060	10683340	0.001065894	-1.027905854	-0.889412828
chr13	73301140	73302520	0.001065801	-1.372077535	-1.113430359
chr20	48428480	48430340	0.001065726	-1.237099156	-1.00116725
chr3	192883060	192885520	0.001065555	-1.428786053	-1.322844775
chr19	39894460	39894780	0.001065426	-1.187715458	-0.996313451
chr6	120401720	120402180	-0.001065284	-1.009549245	-1.233510065
chr6	120401700	120402200	-0.001065284	-1.009549245	-1.233510065
chr4	40619520	40619900	-0.001065136	-0.847431075	-0.990053967
chr8	15633020	15633420	-0.001065105	-0.915016761	-1.171364044
chr1	210000840	210001760	0.001065077	-1.132260504	-1.006573082
chr11	123000120	123000580	-0.00106498	-1.155015901	-1.343874883

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr7	121842240	121842780	-0.001063834	-0.991937899	-1.172896997
chr17	74502140	74503080	0.0010638	-1.175635356	-0.995409738
chr11	34460040	34460640	0.001063626	-1.244403653	-1.06108186
chr11	64014880	64015260	0.001063601	-1.055952472	-0.976471255
chr17	7782040	7782460	-0.001063588	-0.771238911	-0.916943133
chr17	7781960	7782540	-0.001063588	-0.771238911	-0.916943133
chr2	4914080	4914760	-0.001063554	-1.115782401	-1.362849942
chr7	1014620	1015760	0.001063502	-1.332682407	-1.139674366
chr2	224869500	224870020	-0.001063485	-1.121608458	-1.345308212
chr1	91924480	91925140	-0.001062913	-0.988434207	-1.247800755
chr10	119289420	119289880	-0.001062847	-1.041094563	-1.205617396
chr3	30550760	30551360	-0.001062722	-1.074033384	-1.222912042
chr17	11282280	11282740	-0.001062695	-0.843223284	-1.102557041
chr16	12605980	12606500	-0.001062683	-0.955491967	-1.139242583
chr9	81450580	81450980	0.001062223	-1.178520377	-0.997277182
chr3	29371160	29371600	-0.001062193	-0.969882253	-1.251612963
chr1	172501180	172503040	0.001062019	-1.378691639	-1.202672334
chr6	31125400	31126740	0.0010616	-1.275532421	-1.133590191
chr3	78278820	78279320	-0.00106157	-1.20665777	-1.325978123
chr9	98746200	98746760	-0.001061455	-0.85577376	-1.055729949
chr1	155107540	155108940	0.001061352	-1.236326257	-1.065068866
chr1	32538080	32539360	-0.001061303	-0.97766906	-1.045095951
chr1	169706360	169706680	-0.001061262	-0.961621347	-1.243096952
chr13	76396700	76397160	-0.001061199	-1.173925455	-1.320046209
chr1	72766240	72767200	0.001061046	-1.346491081	-1.257503207
chr1	72766240	72767200	0.001061046	-1.346491081	-1.257503207
chr1	53661880	53662980	0.001060978	-1.206076294	-1.037833011
chr7	26207980	26208280	-0.001060572	-0.997341977	-1.158020464
chr7	26207980	26208280	-0.001060572	-0.997341977	-1.158020464
chr9	133587700	133589100	0.001060417	-0.94101629	-0.827412466
chr19	58816180	58817100	0.001060272	-1.173942315	-1.009236523
chr18	40774940	40775360	-0.00106021	-1.026941616	-1.261038438
chr2	238506540	238507100	0.001060157	-1.320035887	-1.114541906
chr2	105200540	105201000	0.00106015	-1.078135131	-0.928193763
chr2	32594760	32595300	-0.001060123	-1.069905578	-1.212855621
chr12	110869660	110870120	-0.001059809	-0.986023797	-1.193076598
chr7	14685820	14686380	-0.001059752	-1.042592464	-1.185601123
chr9	35071820	35073400	0.001059672	-1.168023078	-1.003122186
chr8	126009920	126011160	0.001059389	-1.2835234	-1.091255914
chr1	210110680	210112220	-0.001059239	-0.962066236	-0.989257339
chr17	21156100	21156980	0.001059148	-1.18253498	-0.965354581
chr6	26031260	26031560	-0.001059033	-1.081290913	-1.314958039
chr4	118660820	118661240	-0.001058997	-1.169830156	-1.357892553
chr4	118660820	118661240	-0.001058997	-1.169830156	-1.357892553
chr10	9427700	9428240	-0.00105898	-0.905293485	-1.203393664
chr22	37418060	37418300	0.001058928	-1.030127693	-0.827593202
chr15	68569580	68571240	0.001058791	-1.075288729	-0.934970205
chr13	96328620	96330060	0.001058774	-1.446473859	-1.266739818
chr3	95740640	95741080	-0.001058529	-1.252988882	-1.399572594
chr6	26216520	26217560	0.001058465	-1.191862664	-1.092257409
chr7	46774020	46774560	-0.001058378	-0.941862056	-1.158447808
chr15	69754920	69755500	0.001058136	-1.207111847	-0.992770563
chr5	154412720	154413080	-0.001058102	-1.121563868	-1.291053254
chr5	154412720	154413080	-0.001058102	-1.121563868	-1.291053254
chr10	75531880	75533060	0.001057866	-1.170109273	-0.894167031
chr6	11616900	11618120	-0.001057435	-1.135866592	-1.369043879
chr8	78598540	78599060	-0.001057194	-1.107000595	-1.243146023
chr12	128411460	128411920	0.001057176	-1.283965561	-1.200746793
chr5	36294740	36295260	-0.001057089	-1.044447333	-1.237221841
chr6	42981220	42982560	0.001056974	-1.407680512	-1.257385674
chr8	51278960	51279660	-0.001056695	-1.039352915	-1.304280031
chr16	11680340	11681200	0.001056632	-1.122679556	-0.996384727
chr3	44902720	44904060	0.001056525	-1.24377157	-1.070364239
chr5	89295020	89295520	-0.001055942	-1.068407178	-1.280313917
chr16	60808940	60809460	-0.001055615	-0.960905219	-1.040569046
chr16	60808940	60809460	-0.001055615	-0.960905219	-1.040569046
chr1	240085100	240085620	-0.001055522	-1.100107209	-1.243136578
chr4	132511940	132512460	-0.001055503	-1.174290979	-1.329169268
chr3	193972460	193973140	-0.001055213	-1.1040549	-1.271111533
chr4	84561100	84561400	0.00105502	-1.359227955	-1.122811932
chr4	84560620	84561880	0.00105502	-1.359227955	-1.122811932
chr5	180162520	180163200	-0.001054928	-0.930764908	-1.190277427

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr14	65462220	65462620	-0.001054812	-1.029955404	-1.213119916
chr17	2415040	2415460	0.001054785	-1.073421307	-0.878431761
chr17	70083280	70084160	-0.001054762	-0.840422439	-1.136458952
chr17	70083280	70084160	-0.001054762	-0.840422439	-1.136458952
chr5	180475540	180476080	-0.001054739	-1.176059266	-1.29224788
chr22	45199300	45199880	0.001054419	-1.044819971	-0.898708091
chr6	24581380	24581640	0.001054385	-1.156837084	-0.985477973
chr12	32816300	32816540	0.001054202	-1.157069946	-1.098421716
chr19	41945220	41946520	0.001054171	-1.142778686	-1.017073445
chr6	13820680	13821200	-0.001054512	-1.0183836	-1.237296366
chr7	138795320	138795540	-0.00105407	-0.95259166	-1.095802873
chr7	138795200	138795660	-0.00105407	-0.95259166	-1.095802873
chr8	74205740	74207700	0.001054062	-1.266437646	-1.059859639
chr2	220110020	220110340	0.001053938	-1.294935042	-1.093058622
chr10	15138920	15139760	0.001053861	-1.364591561	-1.187598941
chr15	95783860	95784600	-0.001053785	-1.097385483	-1.282715393
chr7	73963480	73963840	-0.001053728	-0.840794181	-0.990590009
chr5	142812820	142813200	-0.001053667	-1.044501112	-1.284213529
chr16	2569700	2571060	0.001053614	-1.272552672	-1.099963268
chr7	89080940	89081460	-0.001053606	-1.084725687	-1.28482253
chr21	46970660	46971100	0.001053316	-1.205210653	-1.054990352
chr2	64502180	64502640	-0.001053238	-0.870377643	-1.092364105
chr1	20349000	20349360	0.001053204	-0.923967606	-0.969043516
chr2	86796220	86796680	-0.00105314	-0.916241203	-1.124275766
chr20	62169300	62170240	0.0010531	-1.239357951	-1.0917641
chr22	46672420	46673080	-0.001052902	-0.827307748	-1.041129131
chr16	30640120	30640400	0.00105268	-1.116391515	-1.008873486
chr13	50509800	50511420	0.001052663	-1.459747054	-1.250420055
chr4	176557240	176559200	-0.001052534	-1.164248369	-1.379842265
chr15	26521920	26522420	-0.00105236	-0.966202001	-1.217235476
chr18	72920540	72921680	0.001052166	-1.271782813	-1.076891793
chr18	72920540	72921680	0.001052166	-1.271782813	-1.076891793
chr4	1080160	1081380	0.001052116	-1.2263323512	-1.091732508
chr16	88636100	88637400	0.001052098	-1.330903406	-1.161781357
chr9	113913280	113914100	-0.001051937	-0.870674027	-1.139839818
chr20	62710540	62711620	0.001051919	-1.131035301	-1.035979026
chr6	167411640	167413520	0.00105173	-1.314382345	-1.099150256
chr1	59969040	59969540	-0.001051639	-1.007436307	-1.153061663
chr16	34949800	34950160	-0.001051578	-0.792529345	-1.0044325
chr5	81329440	81330060	-0.001051555	-1.078813213	-1.329758415
chr19	7935220	7935820	0.001051412	-1.167761077	-0.998484007
chr4	117793120	117793560	-0.001051298	-1.077207454	-1.287824449
chr13	20534300	20534620	0.001051294	-1.319030802	-1.207032867
chr4	190273440	190274160	0.001050982	-1.037432748	-1.114125884
chr21	24615440	24616040	-0.001050944	-0.884373533	-1.110456905
chr4	94834420	94834820	-0.001050638	-1.024403454	-1.233405774
chr4	94834420	94834820	-0.001050638	-1.024403454	-1.233405774
chr9	131102340	131103480	0.001050457	-1.078808257	-0.878672257
chr15	26521880	26522480	-0.00105045	-0.981726058	-1.210502704
chr4	170139120	170140020	-0.001050445	-1.098048845	-1.317733743
chr12	33388380	33388580	0.001050242	-1.358689159	-1.178523009
chr5	142391860	142392240	-0.001050122	-1.010366161	-1.126460115
chr5	4641340	4641820	-0.001050048	-1.049357907	-1.183513707
chr1	43996240	43997540	-0.001050011	-0.993795294	-1.051836111
chr3	121078640	121079100	-0.001049671	-1.10855977	-1.324536722
chr5	157952120	157952600	-0.001049561	-0.897121959	-1.174393449
chr9	83372340	83373420	-0.001049483	-0.834580183	-1.050214646
chr17	40915480	40915780	0.001049477	-1.087886311	-0.932373982
chr5	65596600	65596880	0.001049316	-1.191586944	-0.986076481
chr2	161349100	161351020	0.00104924	-1.334989767	-1.181955237
chr2	161349080	161351040	0.00104924	-1.334989767	-1.181955237
chr10	5854680	5856060	0.001049027	-1.27734593	-1.134878048
chr2	29308280	29308840	-0.001048929	-1.142272031	-1.364632436
chr2	29308280	29308840	-0.001048929	-1.142272031	-1.364632436
chr22	39333340	39334040	0.001048896	-0.970638658	-0.782262958
chr11	518440	519220	0.001048872	-1.387567932	-1.178343219
chr2	126648800	126649060	-0.001048773	-1.142601142	-1.303093218
chr1	115655460	115655740	0.001048711	-1.227564012	-1.077490343
chr2	75103460	75103720	-0.001048701	-1.039942112	-1.129865086
chr10	97123120	97123400	0.001048658	-1.2218975	-1.081500806
chr19	33403900	33404260	0.001048601	-1.039054655	-1.03105683
chr12	113772760	113773160	0.001048499	-1.290131494	-1.095278831

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr1	210500080	210500500	-0.001048306	-0.996227495	-1.160705944
chr13	114238460	114239880	0.001048278	-1.353233352	-1.160457646
chr1	115631360	115632840	0.001048228	-1.215295542	-1.073467119
chr4	176756560	176757140	0.001048038	-1.267741661	-1.151414268
chr14	34953700	34954120	0.001047922	-1.057368905	-1.09191628
chr2	195611940	195612440	-0.001047885	-0.778437718	-1.027926196
chr1	240085100	240085660	-0.001047754	-1.095250316	-1.240452182
chr8	112037040	112037480	-0.00104759	-1.038691409	-1.293912507
chr15	34385760	34386260	-0.001047464	-0.984287736	-1.146529764
chr10	11149660	11150280	-0.001047451	-1.080606915	-1.231481909
chr15	69109920	69111280	0.001047261	-1.084201115	-0.965159757
chr3	42814060	42815460	0.001047243	-1.256536608	-1.077111924
chr12	27932420	27933820	0.001047096	-1.189247386	-1.052587982
chr9	33288240	33288460	0.001047029	-0.953171773	-0.753821117
chr9	33288240	33288460	0.001047029	-0.953171773	-0.753821117
chr22	42486620	42487260	0.001046271	-1.221148335	-1.088720805
chr22	42486640	42487240	0.001046271	-1.221148335	-1.088720805
chr13	87088980	87090120	-0.00104611	-1.256993779	-1.407430352
chr6	155635020	155636380	0.001046089	-1.325558338	-1.113042836
chr9	73901620	73902280	-0.001045726	-1.02085973	-1.233777496
chr9	19432460	19432920	-0.001045646	-0.884064194	-1.099833131
chr1	9551160	9551440	0.001045488	-1.239031512	-0.991781812
chr3	183903000	183904660	0.00104544	-1.422200466	-1.237315145
chr9	139886300	139887160	0.001045367	-1.152617441	-0.968207988
chr3	47091120	47091620	-0.001045299	-1.223009732	-1.404493284
chr21	34142900	34144700	0.001045213	-1.045825156	-0.93741751
chr12	91288920	91289460	-0.001045192	-1.165412054	-1.324801926
chr15	45906480	45906740	0.001045113	-0.989524142	-0.828891063
chr4	25792020	25792600	-0.001045068	-1.222344757	-1.305864602
chr4	168037060	168038280	-0.001044929	-1.110658799	-1.275995386
chr4	126503820	126504300	-0.001044837	-1.103033332	-1.259425048
chr11	65343220	65343900	0.001044791	-1.380304195	-1.141174136
chr1	66562020	66562440	-0.001044539	-0.920312868	-1.160888226
chr13	38609800	38610660	0.00104434	-1.153969885	-1.187525489
chr21	24493120	24493600	-0.001044044	-1.041730186	-1.243697347
chr16	82163980	82164860	0.001044	-1.140134382	-1.047528024
chr8	109527560	109528100	-0.001043833	-0.960430969	-1.203817408
chr5	60627400	60629780	-0.001043822	-1.245959246	-1.373666286
chr18	50219520	50220020	-0.001043788	-1.076246504	-1.309957788
chr12	75545460	75545960	-0.001043539	-0.887021945	-1.228922708
chr20	40904940	40905360	0.001043497	-1.171588811	-1.052317453
chr20	40904940	40905360	0.001043497	-1.171588811	-1.052317453
chr15	51422960	51423860	0.001043497	-1.063197713	-1.013245248
chr3	105701360	105702080	-0.001043388	-1.081581672	-1.311459979
chr6	139094420	139095340	0.001043374	-1.392269637	-1.26048435
chr19	13262460	13262900	0.001043243	-1.215582025	-1.092441132
chr9	113578380	113578840	-0.001043239	-0.713926174	-0.854864478
chr9	98746260	98746720	-0.001043141	-0.887780016	-1.068501807
chr6	35551640	35551920	0.001043061	-1.239825798	-0.994828173
chr3	178248200	178248600	-0.001042791	-0.982464942	-1.193383167
chr15	37903880	37904300	-0.001042654	-0.837021284	-1.126239515
chr21	40738580	40739120	-0.001042586	-1.037304534	-1.233053819
chr5	22283120	22283700	0.001042419	-1.20705177	-1.140087031
chr8	68130240	68130660	-0.00104238	-1.028420036	-1.282934807
chr19	35631060	35631280	0.001042325	-0.852750804	-0.672366654
chr12	110887520	110888860	-0.001042168	-1.164581556	-1.24214092
chr5	112287580	112288060	-0.001042146	-1.000453775	-1.223758202
chr19	3698760	3699080	0.001042076	-1.021923994	-0.877124593
chr4	110132200	110132580	-0.001041994	-1.055748279	-1.202631411
chr4	14979100	14979620	-0.001041941	-0.93824057	-1.204743542
chr15	49447560	49448140	0.001041906	-1.173472357	-1.065755413
chr7	77427300	77428880	0.00104176	-1.295102022	-1.130363395
chr3	3330800	3331220	-0.001041758	-1.149013268	-1.233159737
chr13	31111540	31112020	-0.001041546	-1.101809387	-1.237286658
chr2	40479740	40480640	-0.001041513	-1.155353365	-1.318833792
chr2	40479720	40480660	-0.001041513	-1.155353365	-1.318833792
chr13	45914600	45915780	0.001041439	-1.265821901	-1.124897095
chr16	58300120	58300500	-0.001041335	-0.902171065	-1.069516835
chr1	202857500	202859000	0.0010413	-1.200470531	-0.980105005
chr22	35834040	35834440	0.001041208	-0.990790247	-0.873137011
chr1	19854460	19854880	-0.001041116	-0.910025256	-1.150156266
chr12	61485460	61485960	0.001040977	-1.18985743	-1.138951983

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr19	45393600	45395080	0.00104093	-1.267322877	-1.134961244
chr2	235860020	235861280	0.001040901	-1.34480983	-1.223342203
chr12	111834500	111835420	0.001040707	-1.191265495	-1.038576313
chr2	37319280	37320020	-0.001040638	-1.031684579	-1.206889664
chr22	50607940	50609320	0.001040482	-1.098601491	-0.938871734
chr13	20915700	20916380	-0.001040321	-1.129477498	-1.364759637
chr2	171688060	171688560	-0.001040286	-1.062519176	-1.18404087
chr18	60506760	60507280	-0.001040249	-1.110013464	-1.250915742
chr13	34102180	34102580	-0.001040243	-1.125029479	-1.27314347
chr19	41480500	41480780	0.001040238	-1.121953431	-0.894125399
chr19	41480440	41480840	0.001040238	-1.121953431	-0.894125399
chr2	6817920	6818320	-0.001040202	-0.940891132	-1.207169307
chr14	99905720	99906420	-0.001040178	-1.079547448	-1.183402158
chr12	88793720	88794180	-0.001039953	-1.123103471	-1.3238514
chr6	137314060	137314300	0.001039629	-1.319164151	-1.197857271
chr11	44578240	44578520	0.001039615	-1.326220835	-1.10452668
chr2	100105740	100107180	0.001039382	-1.338979681	-1.189711002
chr8	98747340	98747700	-0.001039351	-1.029302725	-1.206063553
chr3	110726900	110727420	-0.001039299	-1.059749298	-1.287405257
chr7	42852840	42853320	-0.00103919	-0.979981225	-1.169585842
chr10	33245960	33247860	0.001039184	-1.32719337	-1.100869871
chr8	56792160	56793320	0.001039011	-1.309293693	-1.070084357
chr7	71895040	71895520	0.001038687	-1.041928243	-1.021469528
chr5	126582240	126583000	-0.001038677	-1.082170843	-1.325355207
chr19	16738360	16739780	0.001038453	-1.283490539	-1.176186075
chr7	20854120	20854640	-0.001038266	-1.041103444	-1.224792498
chr6	32938580	32938960	-0.00103815	-0.951695526	-1.134149147
chr11	118868100	118869480	0.001038093	-1.208780602	-1.08224328
chr11	47416300	47416600	0.001038091	-1.291571565	-1.102034512
chr3	13983700	13984040	-0.001038034	-0.923041884	-1.22183192
chr13	69417840	69418420	-0.001038007	-1.052411101	-1.219981931
chr4	74044400	74045920	-0.001037831	-1.111614682	-1.291495981
chr16	15685700	15686140	-0.001037819	-0.887957959	-1.014206782
chr6	40402540	40403060	-0.001037813	-1.081796217	-1.252929869
chr11	90617340	90617760	0.001037698	-1.19782644	-1.178396128
chr1	207970720	207971000	0.001037264	-1.18573116	-0.982429157
chr8	24077280	24077900	-0.001037029	-1.112651916	-1.296607825
chr8	34540220	34540700	0.001036986	-1.150515745	-1.132518307
chr2	60901720	60902020	0.001036728	-1.32922863	-1.046251321
chr8	87647860	87648240	-0.001036632	-1.101584589	-1.312759061
chr20	6308000	6308200	-0.001036567	-0.976286756	-1.164954849
chr20	6308000	6308200	-0.001036567	-0.976286756	-1.164954849
chr16	451400	452040	0.001036543	-1.12034564	-1.002070108
chr16	451400	452040	0.001036543	-1.12034564	-1.002070108
chr3	112027620	112027880	-0.001036332	-0.888787589	-1.139268946
chr3	112027620	112027880	-0.001036332	-0.888787589	-1.139268946
chr11	37766520	37766940	-0.001036094	-1.016119349	-1.274964931
chr12	110561620	110562620	0.001036082	-1.440940338	-1.303532812
chr2	195514940	195515540	-0.001036005	-1.151204714	-1.359104481
chr6	20214060	20214540	-0.001035912	-0.987433481	-1.232278991
chr19	41196020	41197320	0.001035906	-1.242392499	-1.115518264
chr11	70116200	70117420	0.001035744	-1.43554101	-1.292622758
chr12	133107160	133107580	0.001035648	-1.383504114	-1.233437737
chr2	48131620	48134260	0.001035356	-1.187996852	-0.959575841
chr9	99179600	99181720	0.001035356	-1.092968833	-0.930089506
chr2	112942120	112942540	-0.001035206	-0.948227607	-1.15140312
chr7	148292160	148293020	-0.001035105	-1.130457921	-1.38000018
chr1	161456500	161457400	-0.001035036	-1.001964241	-1.036876004
chr11	2554040	2554320	-0.001035014	-1.193281415	-1.225968969
chr22	32725960	32726740	0.001034908	-1.019181714	-0.83650659
chr22	32725960	32726740	0.001034908	-1.019181714	-0.83650659
chr4	58937700	58938140	-0.001034834	-0.983927942	-1.195835967
chr16	25035060	25035580	0.001034659	-1.159405753	-1.072046336
chr12	2049220	2049500	0.001034595	-1.331737592	-1.194250229
chr11	122932400	122933840	0.00103456	-1.348702691	-1.160777434
chr2	194259260	194259760	-0.001034383	-1.074462076	-1.275914347
chr3	81677740	81678140	0.001034162	-1.253881897	-1.239495453
chr22	33589740	33590120	0.001034157	-1.050762477	-1.035386728
chr2	42552540	42553000	-0.001034017	-1.05168832	-1.239253003
chr17	57970020	57971120	0.001033949	-1.091429145	-0.966564914
chr2	194203240	194203740	0.001033807	-1.096273995	-1.029663758
chr4	163469180	163469620	-0.001033723	-0.957154606	-1.214545702

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr22	39189580	39190860	0.001033622	-1.047710713	-0.894548937
chr3	106229840	106230140	-0.001033365	-0.967647274	-1.238896988
chr5	178157160	178158460	0.001033248	-1.281474656	-1.097339286
chr2	12812100	12812580	-0.001033086	-1.182115198	-1.248527541
chr19	56577680	56578200	0.001032968	-1.039189521	-0.863250323
chr5	147416380	147416920	0.001032816	-1.232594579	-1.152383676
chr20	33146120	33147400	0.001032689	-1.234567853	-1.078360152
chr4	69479340	69479620	0.001032608	-1.389476181	-1.161690336
chr1	35578020	35578380	-0.001032597	-0.983034952	-1.189838033
chr3	48507040	48508060	0.001032501	-1.188477899	-1.034494566
chr19	42103660	42104560	0.001032413	-1.151407518	-0.974207826
chr22	20118540	20119940	0.001032413	-1.196362526	-1.064698973
chr10	103588960	103590000	0.001032343	-1.345878961	-1.183846032
chr17	16120340	16120640	0.001032166	-1.112941546	-1.001057351
chr17	16120340	16120640	0.001032166	-1.112941546	-1.001057351
chr1	21835200	21836680	0.001032158	-1.105907004	-0.923563436
chr19	1478480	1479780	0.00103215	-1.134522824	-0.932762276
chr5	7395680	7396900	-0.001031985	-1.187239075	-1.304303221
chr11	14771220	14771600	-0.001031847	-1.077002299	-1.24753692
chr19	4400060	4400900	0.00103182	-1.203576894	-1.066076469
chr7	123630980	123631340	-0.001031537	-0.775144349	-1.05470345
chr19	44258580	44259600	0.001031414	-1.106293118	-0.982902709
chr2	229128100	229128500	-0.001031312	-0.916710877	-1.072561928
chr2	148517700	148518140	-0.001031295	-1.0886611656	-1.207613907
chr2	82475320	82475760	0.00103126	-1.142342052	-1.064927753
chr7	143594020	143594440	0.001031184	-1.224425702	-1.117740071
chr20	17996720	17997100	0.001031123	-1.17668744	-1.14564244
chr1	89989780	89991160	0.001031115	-1.185691673	-0.96800612
chr17	56415380	56415940	0.001030957	-1.008509474	-0.825503978
chr17	56415280	56416040	0.001030957	-1.008509474	-0.825503978
chr12	99038200	99039600	0.001030954	-1.399710594	-1.254802698
chr7	57830840	57831140	0.001030918	-1.102409121	-1.015419231
chr7	57830840	57831140	0.001030918	-1.102409121	-1.015419231
chr7	74931700	74932240	-0.001030887	-1.084806329	-1.273153773
chr12	113857220	113857720	-0.001030785	-1.032787104	-1.278383652
chr5	32612920	32613860	0.001030719	-1.310395077	-1.071083311
chr5	105900100	105900740	-0.001030473	-1.098013661	-1.274695798
chr7	44269880	44271700	0.001030411	-1.23484413	-1.091094114
chr12	133107140	133107680	0.001030388	-1.283570655	-1.176590817
chr1	64971020	64971860	0.001030267	-1.15372054	-0.90707651
chr1	243389120	243389700	-0.001030237	-1.022703847	-1.207192668
chr2	57096460	57096920	0.001029942	-1.199710091	-1.140910457
chr11	728900	729200	0.001029933	-1.167755472	-0.929969125
chr6	126902860	126903300	-0.001029852	-1.103744433	-1.257122752
chr19	442800	443340	0.001029454	-1.066200999	-0.874960838
chr19	442800	443340	0.001029454	-1.066200999	-0.874960838
chr2	115933680	115934040	-0.001029372	-0.854210626	-1.181471853
chr2	115933600	115934120	-0.001029372	-0.854210626	-1.181471853
chr1	44382900	44383840	-0.001029336	-0.994577154	-1.123504451
chr7	155725060	155726240	0.001029272	-1.099637069	-1.013534241
chr4	55588800	55589200	-0.001029054	-1.010383027	-1.250259292
chr1	26535180	26535640	-0.001028883	-0.999654482	-1.14337468
chr5	133702440	133704000	0.001028589	-1.194858041	-0.932415791
chr10	128460120	128460540	0.001028522	-1.269754236	-1.165125838
chr4	158667240	158667760	-0.001028516	-1.123099199	-1.342229646
chr16	2801340	2803360	0.001028246	-1.103195751	-0.944174733
chr10	63590960	63592100	-0.001028075	-1.000925287	-1.302506495
chr1	205718380	205719640	0.001028024	-1.187211456	-1.011390017
chr14	41442740	41443120	-0.001027999	-0.834424532	-1.151072491
chr2	115329180	115329760	-0.001027977	-1.016553976	-1.261079621
chr19	46532040	46532580	0.001027648	-1.166634719	-1.017660851
chr12	130122860	130123380	-0.001027627	-1.098319466	-1.300844747
chr1	72153860	72154240	-0.001027345	-1.043991741	-1.287563684
chr5	176856260	176856500	0.001027325	-1.218106147	-0.985866379
chr8	558800	559580	0.001027217	-1.265865125	-1.134717252
chr18	558800	559580	0.001027217	-1.265865125	-1.134717252
chr2	122512620	122513660	0.001027179	-1.262774997	-1.101386422
chr16	8837080	8837780	-0.001027066	-0.958782174	-1.222570549
chr7	53655860	53656200	0.001026913	-0.940613069	-0.941534123
chr3	141456280	141457940	0.001026709	-1.261672944	-1.163874163
chr18	65551880	65552340	-0.001026662	-1.090279209	-1.237656756
chr18	65551860	65552360	-0.001026662	-1.090279209	-1.237656756

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr8	113911520	113912200	-0.001026639	-1.035516716	-1.108868283
chr4	175364180	175364620	-0.001026606	-1.038747485	-1.236018402
chr2	196290480	196291280	-0.001026577	-1.144756361	-1.323924441
chr4	118564540	118565000	-0.001026557	-1.032385384	-1.228991905
chr22	19466420	19468000	0.00102654	-1.11321642	-0.931133504
chr8	67691780	67692080	-0.001026468	-1.048689298	-1.217225507
chr4	126094340	126095320	0.001026454	-1.331856469	-1.286911075
chr7	33227520	33227960	0.001026366	-1.229993732	-1.085175185
chr18	64538620	64539100	-0.001026358	-1.220387336	-1.363822694
chr7	141654840	141655220	-0.001026259	-0.889678906	-1.098059566
chr11	32558760	32559180	-0.001026173	-1.130214121	-1.229414349
chr6	83935600	83935920	-0.00102608	-0.824706684	-1.027714009
chr15	67134720	67135420	-0.001026016	-0.98192262	-1.028246363
chr16	4303680	4304480	0.001025944	-1.290512611	-1.155569003
chr16	4303660	4304480	0.001025944	-1.290512611	-1.151451581
chr19	41859440	41860180	0.001025822	-1.249359992	-1.112027877
chr7	1618800	1620680	0.001025676	-1.299128418	-1.207645436
chr8	125126920	125127340	-0.001025662	-1.006175005	-1.237873637
chr12	109197020	109197960	0.001025294	-1.328119341	-1.15990534
chr2	150633720	150634180	-0.001025231	-0.990424918	-1.164779955
chr3	48481100	48481940	-0.001025161	-1.057974952	-1.12703377
chr2	141060420	141060820	-0.00102509	-0.845065315	-1.055739593
chr2	141060420	141060820	-0.00102509	-0.845065315	-1.055739593
chr10	83106120	83106640	-0.001024914	-1.021719329	-1.254470515
chr11	68038660	68040180	0.001024702	-1.41734785	-1.228679402
chr22	38054000	38055860	-0.00102461	-0.928621306	-1.026628225
chr9	9550240	9550700	-0.00102448	-0.754560584	-0.962847463
chr4	155223780	155224160	0.001024248	-1.170344463	-1.033833169
chr1	1231980	1232500	0.001024212	-1.220714262	-1.063522523
chr6	22432680	22433120	-0.001023972	-1.029123544	-1.247679758
chr20	25227680	25229500	0.001023886	-1.096190688	-0.934927635
chr14	81678080	81678480	-0.001023822	-0.839128079	-1.055570223
chr11	67454620	67455180	-0.001023763	-1.092980776	-1.203664623
chr1	167708280	167708760	-0.001023684	-0.911899226	-1.102536445
chr2	74691420	74692700	0.001023519	-1.095949405	-0.860196555
chr1	89823920	89824180	0.001023487	-1.049022903	-0.917053793
chr16	47494700	47495680	0.00102336	-1.199216958	-0.932257389
chr9	134406000	134407240	0.00102325	-1.20889948	-0.991442093
chr5	96142920	96144280	0.001023213	-1.274098331	-1.096493074
chr5	169170700	169171100	0.001023193	-1.100807745	-1.033387657
chr6	98099480	98099880	-0.001023178	-1.055482443	-1.197524783
chr9	102863240	102863560	0.001022946	-0.890814569	-0.843650022
chr7	128734340	128734780	-0.001022854	-1.10320279	-1.238110342
chr3	120461020	120462000	0.001022846	-1.249691561	-1.169671394
chr14	104602540	104602900	-0.001022713	-1.054085585	-1.15497804
chr15	43476880	43478200	0.001022667	-1.196792092	-1.028497681
chr11	65626820	65627120	0.001022664	-1.326652303	-1.201267222
chr4	14379060	14379520	-0.001022517	-1.01552109	-1.202764697
chr4	14379040	14379540	-0.001022517	-1.01552109	-1.202764697
chr12	2049200	2049500	0.001022365	-1.358512602	-1.205921856
chr7	105516520	105517800	0.001022307	-1.347632287	-1.186694098
chr1	27935180	27935900	-0.00102199	-0.86459284	-0.973894861
chr1	107379020	107379600	-0.001021922	-1.005389283	-1.228177914
chr2	210288180	210289000	0.001021796	-1.106099403	-0.946424793
chr1	14840800	14841340	-0.001021785	-1.208605665	-1.343408096
chr20	62710260	62711860	0.001021777	-1.131035301	-1.039988432
chr10	24809340	24809840	0.001021737	-1.162491528	-1.075068847
chr12	14518220	14519420	0.001021685	-1.183875176	-1.094126643
chr7	61817480	61817460	0.001021613	-1.149009357	-1.099336128
chr22	46645720	46646920	0.001021552	-0.980070435	-0.788707327
chr9	35646740	35647700	-0.001021479	-0.96281032	-0.935692683
chr2	58655200	58656220	0.001021343	-1.16715441	-0.95208301
chr1	89989840	89991120	0.001021329	-1.185691673	-0.963985905
chr15	64125500	64126780	0.001021251	-1.136823878	-0.927147206
chr1	40008380	40008700	-0.001021233	-0.971823031	-1.10984453
chr11	25671780	25673580	-0.001021119	-1.015051533	-1.134510231
chr1	96776640	96777160	-0.001020886	-0.953040012	-1.148267504
chr6	102152680	102153040	-0.001020874	-0.981697375	-1.24456729
chr6	102152640	102153080	-0.001020874	-0.981697375	-1.24456729
chr19	14543900	14544780	0.001020805	-1.110089518	-0.990607081
chr10	102480700	102481080	-0.001020764	-0.940136749	-1.183348158
chr5	2377760	2378300	0.001020618	-1.336078594	-1.166885814

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr19	14674960	14675540	0.001020588	-1.149769137	-1.016194888
chr8	138959600	138960040	-0.00102056	-1.037467089	-1.26642139
chr8	138959580	138960060	-0.00102056	-1.037467089	-1.26642139
chr2	175819740	175820080	-0.001020511	-0.901979661	-1.190676982
chr2	175819740	175820080	-0.001020511	-0.901979661	-1.190676982
chr5	167218260	167218700	-0.00102047	-1.178437129	-1.357443957
chr5	78833880	78834340	-0.001020343	-1.067296953	-1.290186498
chr2	67874600	67875100	-0.001019968	-1.048975807	-1.248735705
chr6	84427000	84427860	0.001019918	-1.244157619	-1.055887387
chr7	138326360	138326800	-0.001019861	-1.016714782	-1.192906916
chr6	11575780	11576100	0.001019815	-1.201267545	-1.018782664
chr11	87356620	87357480	-0.001019771	-1.157587052	-1.239433255
chr21	35573780	35574920	-0.001019686	-0.792544464	-0.87933119
chr8	10609500	10610100	-0.001019648	-1.004819958	-1.236399658
chr4	135668400	135668700	-0.001019611	-0.948179449	-1.121191348
chr1	102931500	102932280	-0.001019278	-1.166775135	-1.347543815
chr1	194273000	194273300	-0.001019251	-0.958853209	-1.080023133
chr1	219102200	219102900	-0.00101922	-1.088883108	-1.312016085
chr3	175898800	175899060	-0.001019098	-1.052190731	-1.22821285
chr3	175898800	175899060	-0.001019098	-1.052190731	-1.22821285
chr2	129623960	129624640	-0.001018974	-0.93634957	-1.169199021
chr16	4233040	4233260	0.001018665	-0.962961674	-0.829253672
chr13	54076100	54076600	-0.001018645	-1.118501791	-1.213665688
chr16	57118200	57118480	0.001018591	-1.164007036	-0.954553419
chr15	102191500	102193500	0.001018485	-1.114023095	-0.9245272
chr2	216973440	216974680	0.001018482	-1.313716023	-1.22282747
chr4	75353900	75354280	-0.001018083	-0.927711417	-1.142971729
chr12	10656720	10657280	-0.001017911	-1.096839235	-1.263721042
chr2	64401260	64401720	-0.001017756	-0.922663582	-1.19567174
chr9	18287220	18287860	-0.001017716	-0.701714733	-1.007670719
chr11	32913680	32915120	0.001017485	-1.212505213	-1.036128368
chr15	74731120	74731360	0.001017412	-1.098242884	-0.92098896
chr19	19174220	19175380	0.001017399	-1.173187964	-0.97638886
chr6	8819380	8819780	0.001017144	-1.341609093	-1.211854501
chr4	181936880	181937440	-0.001017136	-1.212959697	-1.371983397
chr15	34658600	34660080	0.001017117	-1.041992986	-0.852053098
chr15	67327580	67328380	-0.001017067	-1.043835059	-1.161520109
chr4	178191440	178191860	0.001017066	-1.160753242	-1.170190138
chr6	28023200	28023880	-0.001017065	-1.133323283	-1.323551044
chr6	119194140	119194560	-0.001016799	-1.05863682	-1.166103372
chr1	193028040	193028880	0.001016692	-1.174941757	-0.991913303
chr17	32073080	32073680	-0.001016576	-0.86061877	-1.091467541
chr6	66078980	66079440	-0.001016494	-1.135243792	-1.327667374
chr6	132624680	132625260	-0.001016459	-1.22152905	-1.323860142
chr2	231917180	231918380	0.001016439	-1.246300467	-1.035100581
chr1	92788340	92788800	-0.001016229	-1.033600356	-1.231264495
chr8	98655840	98657040	0.001016178	-1.274194252	-1.162889925
chr15	45926820	45927360	0.001016149	-1.022263356	-0.869739091
chr3	161408400	161408760	0.00101586	-1.29574725	-1.203958632
chr6	117291220	117291700	-0.00101584	-1.11357564	-1.350420543
chr5	3789420	3790120	-0.001015737	-1.14385195	-1.319712924
chr1	200042180	200042700	-0.001015691	-0.9655526	-1.155153817
chr11	20384800	20385800	0.001015663	-1.076643285	-0.909751866
chr17	80019720	80020080	-0.001015657	-0.879488388	-0.973151812
chr5	162671200	162671660	0.001015289	-1.221427999	-1.137906818
chr6	19406720	19407020	-0.001015234	-1.129023432	-1.230412833
chr6	19406720	19407020	-0.001015234	-1.129023432	-1.230412833
chr16	28935540	28937000	0.001015138	-1.205677908	-1.041256966
chr8	90423060	90423520	-0.001014966	-1.272793494	-1.421836796
chr1	206864640	206865040	-0.001014867	-0.863026962	-1.109267795
chr20	21283280	21284660	0.001014755	-1.346610617	-1.215653689
chr2	175009420	175009900	-0.001014719	-0.97493065	-1.129866201
chr7	2302900	2303640	0.001014697	-1.054256336	-0.914218233
chr10	43904240	43904980	0.001014509	-1.228754051	-1.046849396
chr2	117801200	117802760	0.001014488	-1.20338275	-1.19667025
chr11	14771200	14771640	-0.001014482	-1.05748685	-1.242515985
chr20	57276020	57276640	-0.001014467	-1.079612821	-1.200580563
chr17	38136140	38137760	0.001014349	-1.101004058	-1.005079851
chr3	183902960	183904460	0.001014304	-1.263726965	-1.116253901
chr9	104000040	104000780	0.001013962	-1.089871245	-1.015343003
chr9	104000040	104000780	0.001013962	-1.089871245	-1.015343003
chr1	119742840	119743360	-0.001013651	-0.866124866	-1.059701924

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr16	67970640	67970840	0.001013606	-0.992272669	-0.877880738
chr7	128065880	128066160	0.001013571	-1.218630168	-1.022511232
chr7	128065880	128066160	0.001013571	-1.218630168	-1.022511232
chr19	42755420	42755740	0.001013567	-1.108454493	-0.892627416
chr6	162442160	162442440	-0.001013526	-1.034031618	-1.198551186
chr1	72767480	72768440	0.001013416	-1.380122607	-1.25925047
chr5	180475540	180476140	-0.001013371	-1.193629215	-1.352503753
chr2	198227020	198227620	0.001013322	-1.220711209	-1.196552973
chr2	157189140	157189440	-0.001013166	-1.079540428	-1.136234403
chr6	91775400	91775940	-0.001013149	-1.215955463	-1.378522342
chr15	59729960	59730720	-0.001013123	-0.967470823	-1.111478954
chr5	21418020	21418700	-0.001013106	-1.1056096	-1.308333347
chr20	48802800	48803080	0.001012923	-1.338209917	-1.179401773
chr14	104387740	104388140	0.001012896	-1.301831253	-1.125976228
chr17	66461840	66463060	0.001012635	-1.102238386	-0.985360949
chr7	66461840	66463060	0.001012635	-1.102238386	-0.985360949
chr12	56693680	56694760	0.001012583	-1.303877842	-1.181489037
chr3	75211280	75211800	-0.001012506	-1.136755266	-1.345321722
chr3	75211260	75211820	-0.001012506	-1.136755266	-1.345321722
chr1	113161620	113163060	0.001012342	-1.185945793	-0.992810382
chr1	12079160	12080020	0.00101221	-1.159681637	-1.059362816
chr7	85827800	85828200	-0.001012184	-1.056903045	-1.261888921
chr2	12634540	12635500	-0.001011998	-0.969924395	-1.23132418
chr18	76828620	76829840	0.001011876	-1.406630739	-1.241781564
chr4	93109400	93109820	-0.001011848	-0.987773145	-1.151817442
chr2	113506980	113507900	0.001011798	-1.320502199	-1.094966569
chr10	121484780	121486420	0.001011751	-1.322097292	-1.178694009
chr3	78731340	78732120	-0.001011655	-0.958296145	-1.268480246
chr4	33393100	33393600	-0.001011546	-1.005022371	-1.237464653
chr2	12636780	12637240	-0.001011263	-0.920971208	-1.142954662
chr17	45743660	45744020	-0.001011199	-0.979137851	-1.152829987
chr7	45743660	45744020	-0.001011199	-0.979137851	-1.152829987
chr9	105798660	105799240	-0.001010893	-0.975435893	-1.127261442
chr4	30349780	30350160	-0.001010453	-1.133815415	-1.316728757
chr3	187863740	187864220	-0.001010363	-1.0982954	-1.330412527
chr8	21595460	21595940	-0.001010362	-1.18615074	-1.279957653
chr4	63326960	63327360	-0.00101025	-1.06193471	-1.212761529
chr1	154932100	154932360	0.001010173	-1.001658423	-0.830862969
chr3	29336560	29337140	-0.001010154	-1.004780457	-1.276238019
chr12	23990820	23991340	-0.001010102	-1.151804848	-1.343662044
chr1	196405900	196406580	-0.001010018	-1.06705074	-1.253707223
chr22	18303380	18304020	-0.001010009	-0.838842472	-1.141830555
chr9	125112880	125113180	0.001009951	-1.140259229	-0.961214066
chr4	84614340	84615260	-0.001009927	-1.049482284	-1.308179291
chr10	129150260	129150760	0.00100991	-1.311218418	-1.14706214
chr13	47696840	47697600	-0.001009883	-1.079096602	-1.261650169
chr19	1069220	1069420	0.001009793	-1.136707435	-0.967583896
chr5	71615500	71616640	0.001009767	-1.25511121	-1.154674386
chr5	71615500	71616640	0.001009767	-1.25511121	-1.154674386
chr3	171356800	171357720	-0.00100976	-1.239107755	-1.428719752
chr1	10475140	10476120	0.001009727	-1.037826033	-0.950913662
chr9	130533260	130534080	-0.001009265	-0.992851999	-0.053859192
chr7	7513060	7513500	-0.001009104	-0.926304366	-1.136086571
chr21	29028060	29028580	-0.001009028	-0.957779747	-1.131237833
chr7	61836880	61837120	0.001009007	-1.07198452	-0.955191516
chr13	49070720	49071180	-0.001008956	-1.213520767	-1.279422973
chr13	49070700	49071200	-0.001008956	-1.213520767	-1.279422973
chr6	92202740	92203280	-0.001008941	-1.028920515	-1.124676326
chr13	88557580	88558180	0.001008919	-1.200697738	-1.195004659
chr9	24829320	24829720	-0.001008843	-0.847873111	-1.050566463
chr1	240061460	240061760	0.001008688	-1.19495552	-1.028672627
chr15	54845420	54845920	-0.001008669	-1.035279639	-1.287599904
chr22	19577000	19577500	-0.001008668	-0.928456663	-1.063350698
chr6	163368120	163368840	-0.001008651	-1.169777332	-1.405738799
chr9	75018580	75019120	0.001008612	-0.854194818	-0.78049023
chr5	1008580	1009880	0.001008417	-1.280792516	-1.03968813
chr15	24957340	24957960	-0.001008294	-0.774594736	-1.067734406
chr11	47663760	47664460	0.00100814	-1.329506984	-1.204809685
chr11	47663740	47664480	0.00100814	-1.329506984	-1.204809685
chr12	48172800	48173700	0.001008121	-1.273961001	-1.104097671
chr13	48702060	48702500	-0.001008081	-1.004683606	-1.124167011
chr6	48987420	48988300	-0.001008082	-1.025967069	-1.143308576

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr3	34536640	34537140	-0.00100788	-1.027346004	-1.255639467
chr6	12168200	12168820	-0.001007861	-1.23263709	-1.39083466
chr7	149019780	149020280	-0.00100779	-1.033784385	-1.253547421
chr13	64464480	64465100	-0.001007676	-1.181077346	-1.30774886
chr2	45208760	45209100	0.001007585	-1.220906561	-1.017234054
chr2	145168400	145168920	-0.001007411	-1.169680092	-1.286762256
chr4	8862500	8862900	0.001007038	-1.209169838	-0.981010434
chr7	43972300	43972900	-0.001006717	-0.989962168	-1.187321166
chr12	89095440	89096480	-0.0010065	-1.217710385	-1.415272939
chr12	89095440	89096480	-0.0010065	-1.217710385	-1.415272939
chr15	64647820	64648920	0.001006379	-1.09242789	-0.948708046
chr15	89973640	89974580	0.001006341	-1.270409552	-1.06288028
chr1	16173900	16174980	0.001006259	-1.127256665	-0.90392289
chr10	13814040	13814380	-0.001006116	-1.0373272	-1.240421244
chr9	140386720	140387520	0.001005968	-0.994303639	-0.858371755
chr4	177728260	177729300	-0.001005889	-1.031818819	-1.217851673
chr8	8183440	8183920	-0.001005881	-1.041440323	-1.260667888
chr11	112096640	112098140	0.001005871	-1.196978581	-1.022234572
chr21	38494520	38494960	0.00100587	-0.977480167	-0.900200518
chr21	38494520	38494960	0.00100587	-0.977480167	-0.900200518
chr14	95987060	95987580	-0.0010056	-0.987358711	-1.133439845
chr20	34580680	34580960	0.00100559	-1.256999422	-1.169635497
chr8	87442800	87443800	-0.001005392	-1.135346445	-1.356350131
chr16	67875720	67876780	0.001005264	-1.090281104	-0.963365235
chr13	86732900	86733440	-0.001005214	-1.079694044	-1.309331558
chr5	90976520	90977100	-0.00100512	-1.005793249	-1.243888282
chr5	33272940	33273440	-0.001005115	-1.209722679	-1.391984423
chr16	67595800	67597480	-0.001005113	-0.971644616	-1.079401489
chr22	37623540	37623920	0.001005078	-1.061439863	-0.89549802
chr21	35565360	35565820	-0.001004833	-0.774469838	-0.937483305
chr10	101891180	101891620	-0.001004752	-0.91044846	-1.129118981
chr19	47742680	47743180	0.001004649	-1.086706347	-0.934225392
chr2	157247120	157247660	-0.001004553	-0.935213989	-1.154603676
chr2	185889180	185889700	-0.001004481	-1.053135379	-1.185339088
chr14	43955800	43956360	-0.001004456	-1.007575707	-1.237819625
chr5	77655460	77657200	0.001004307	-1.242532213	-1.068457956
chr3	196438700	196439640	0.001004256	-1.410483211	-1.23411157
chr11	25541420	25541860	-0.001004216	-1.027059754	-1.210399672
chr2	103369760	103370640	0.001004157	-1.321167537	-1.073911315
chr13	90246960	90247500	0.001004101	-1.156487579	-1.179515792
chr14	74216120	74216440	-0.001004003	-1.02027969	-1.207744134
chr14	74216080	74216480	-0.001004003	-1.02027969	-1.207744134
chr3	115716320	115717180	-0.001003965	-1.072347288	-1.305694955
chr21	43298640	43299780	-0.001003836	-1.017412577	-1.140110725
chr12	125398540	125399940	0.001003825	-1.414576153	-1.277410922
chr10	131934000	131935300	0.001003665	-1.316522535	-1.19432308
chr10	63590980	63592040	-0.001003566	-1.016792547	-1.29348878
chr2	149087440	149087900	0.001003408	-1.217109733	-1.08930448
chr11	92144060	92144480	-0.00100339	-1.062400463	-1.332528499
chr6	141809960	141810500	-0.001003338	-0.875293236	-1.046101194
chr6	33086100	33086940	0.001003326	-1.229502575	-1.031989926
chr5	145029900	145030340	-0.001003292	-1.109252643	-1.330173993
chr7	98910580	98910840	0.001003095	-1.220827754	-1.034872113
chr12	104234100	104235920	-0.001003092	-1.192533134	-1.297126725
chr3	87149880	87150580	-0.001003081	-1.264797194	-1.443592916
chr3	87149880	87150580	-0.001003081	-1.264797194	-1.443592916
chr7	36584380	36585180	0.001003001	-0.959239556	-0.808465772
chr2	54197460	54198680	0.001002833	-1.326492659	-1.11621836
chr2	58121140	58121520	-0.001002671	-1.177527383	-1.292765373
chr17	80106020	80107200	0.001002509	-1.357373055	-1.232140268
chr5	157936700	157937220	-0.00100246	-1.01361207	-1.256064636
chr19	55615500	55615800	0.001002398	-0.951972522	-0.960227153
chr19	55615500	55615800	0.001002398	-0.951972522	-0.960227153
chr20	61680020	61681040	0.001002369	-1.29490833	-1.174780136
chr4	26514440	26514880	0.001002288	-1.240209995	-1.136545969
chr20	42273680	42273940	0.001002236	-1.356318662	-1.154622253
chr20	42273680	42273940	0.001002236	-1.356318662	-1.154622253
chr8	917520	918040	0.001002188	-1.365560046	-1.256085493
chr21	47488260	47489600	0.001002108	-1.139641014	-0.959148742
chr17	74068280	74068840	0.001002076	-1.173151042	-1.029670449
chr4	38677200	38677480	0.001002062	-1.294617492	-1.139306021
chr5	11623680	11624180	-0.001001915	-0.97687628	-1.164851555

TABLE S4-continued

Most informative fragmentation hotspot location in between HCC and Healthy					
Chromosome id	Start	End	Coefficient in SVM	Mean IFS (z-score) in healthy samples	Mean IFS (z-score) in HCC samples
chr19	19806280	19806480	-0.001001908	-0.672733565	-0.792319746
chr19	19806280	19806480	-0.001001908	-0.672733565	-0.792319746
chr6	103549460	103549720	-0.00100188	-1.172536528	-1.379599301
chr11	127932140	127932700	0.001001794	-1.325074865	-1.218978895
chr12	56497600	56498940	0.001001637	-1.373916704	-1.225679595
chr15	78251760	78251980	-0.001001003	-0.887390899	-0.953858136
chr15	78251760	78251980	-0.001001003	-0.887390899	-0.953858136
chr4	113065780	113067420	0.001000957	-1.303689311	-1.113843912
chr2	220143540	220144780	0.001000908	-1.290872203	-1.090618809
chr5	139813860	139814320	-0.001000652	-0.956373417	-1.181754521
chr10	19594520	19595640	-0.001000638	-1.050449724	-1.265838906
chr15	48581440	48581760	-0.001000483	-0.922670407	-1.050925694
chr14	24802840	24803160	0.001000439	-1.24820447	-1.047162907
chr15	81397260	81397780	0.001000056	-1.079324438	-0.933330338

TABLE S5

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)							
# Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ	Genes
GO Biological Process	GO:0002446	neutrophil mediated immunity	6	8.32E-09	1.07E-04	1.79E-05	ADAM17, APAF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, COTL1, CPNE3, CREG1, CRISPLD2, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LPCAT1, MAN2B1, MANBA, MLEC, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SCAMP1, SERPINB1, SIGLEC5, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VCP, XRCC5
GO Biological Process	GO:0002274	myeloid leukocyte activation	7	1.07E-08	1.37E-04	1.96E-05	ADAM9, APAF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, COTL1, CPNE3, CREG1, CRISPLD2, CRTC3, CTSZ, DHRS2, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LPCAT1, LYN, MAN2B1, MANBA, MAPT, MLEC, NDRG1, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLEKHO2, PRCP, PRDX6, PREX1, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SBNO2, SCAMP1, SERPINB1, SIGLEC5, SLAMF1, SLC2A3, SPII, STK10, SVIP, TGFBI, TIMP2, TMC6, TMEM179B, TOLLIP, TRAF6, TRPM2, TUBB, UBR4, VAMP2, VCP, XRCC5
GO Biological Process	GO:0002275	myeloid cell activation involved in immune response	4	6.09E-09	7.86E-05	1.97E-05	APAF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, COTL1, CPNE3, CREG1, CRISPLD2, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1,

TABLE S5-continued

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)

# Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ	Genes
GO Biological Process	GO: 0036230	granulocyte activation	5	7.80E-09	1.01E-04	2.01E-05	ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LPCAT1, LYN, MAN2B1, MANBA, MLEC, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SBNO2, SCAMP1, SERPINB1, SIGLEC5, SLAMF1, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VAMP2, VCP, XRCC5
GO Biological Process	GO: 0042119	neutrophil activation	8	1.42E-08	1.83E-04	2.29E-05	APAF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, COTL1, CPNE3, CREG1, CRISPLD2, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LPCAT1, MAN2B1, MANBA, MLEC, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLEKHO2, PRCP, PRDX6, PREX1, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SCAMP1, SERPINB1, SIGLEC5, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VAMP2, VCP, XRCC5
GO Biological Process	GO: 0035720	intracellular anterograde transport	9	1.77E-08	2.28E-04	2.54E-05	IFT52
GO Biological Process	GO: 0002283	neutrophil activation involved in immune response	3	6.08E-09	7.84E-05	2.61E-05	APAF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, COTL1, CPNE3, CREG1, CRISPLD2, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LPCAT1, MAN2B1, MANBA, MLEC, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SCAMP1, SERPINB1, SIGLEC5, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VCP, XRCC5

TABLE S5-continued

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)

# Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ	Genes
GO Biological Process	GO: 0043299	leukocyte degranulation	2	5.63E-09	7.26E-05	3.63E-05	APAF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, CORO1A, COTL1, CPNE3, CREG1, CRISPLD2, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LPCAT1, LYN, MAN2B1, MANBA, MLEC, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SCAMP1, SERPINB1, SIGLEC5, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VAMP2, VCP, XRCC5
GO Biological Process	GO: 0002444	myeloid leukocyte mediated immunity	10	3.76E-08	4.85E-04	4.85E-05	ADAM17, APAF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, COTL1, CPNE3, CREG1, CRISPLD2, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LPCAT1, LYN, MAN2B1, MANBA, MLEC, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SCAMP1, SERPINB1, SIGLEC5, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VAMP2, VCP, XRCC5
GO Biological Process	GO: 0043312	neutrophil degranulation	1	3.95E-09	5.10E-05	5.10E-05	APAF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, COTL1, CPNE3, CREG1, CRISPLD2, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LPCAT1, MAN2B1, MANBA, MLEC, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SCAMP1, SERPINB1, SIGLEC5, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VCP, XRCC5
GO Biological Process	GO: 0002366	leukocyte activation involved in immune response	11	6.56E-08	8.47E-04	7.70E-05	ABL1, APAF1, APBB1IP, ATG7, ATP11B, ATP6V0C, B4GALT1, BCL3, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, CORO1A, COTL1, CPNE3, CREG1, CRISPLD2, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERCC1, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LCP1, LFNG, LPCAT1, LYN, MAN2B1, MANBA, MFNG, MLEC, MSH2, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLCG2, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2,

TABLE S5-continued

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)							
# Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ	Genes
GO Biological Process	GO:0002263	cell activation involved in immune response	12	1.56E-07	2.01E-03	1.68E-04	PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SBNO2, SCAMP1, SEMA4A, SERPINB1, SIGLEC5, SLAMF1, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VAMP2, VCP, XRCC5
GO Biological Process	GO:0042026	protein refolding	14	1.96E-07	2.53E-03	1.81E-04	ABL1, APAF1, APBB1IP, ATG7, ATP11B, ATP6V0C, B4GALT1, BCL3, CAT, CCT8, CD300A, CD58, CD97, CKAP4, CNN2, CORO1A, COTL1, CPNE3, CREG1, CRISPLD2, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ERCC1, ERP44, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LCP1, LFNG, LPCAT1, LYN, MAN2B1, MANBA, MFNG, MLEC, MSH2, NPC2, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLCG2, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SBNO2, SCAMP1, SEMA4A, SERPINB1, SIGLEC5, SLAMF1, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VAMP2, VCP, XRCC5
GO Biological Process	GO:0002252	immune effector process	13	1.95E-07	2.52E-03	1.94E-04	BAG1, DNAJB12, DNAJB2, HSP90AA1, HSPA8
GO Biological Process	GO:0002443	leukocyte mediated immunity	15	2.33E-07	3.01E-03	2.01E-04	ABCF3, ABI1, ABL1, ACTB, ADAM17, ADARB1, APAF1, APBB1IP, APOBEC3A, ARPC1A, ATG7, ATP11B, ATP6V0C, B4GALT1, BAIAP2, BCL3, BRK1, C19orf66, CAT, CCT8, CD247, CD300A, CD46, CD58, CD74, CD97, CKAP4, CNN2, CNOT7, CORO1A, COTL1, CPNE3, CREG1, CRISPLD2, CRK, CTSZ, DLG1, DNAJC13, DNAJC3, DOCK1, DOCK2, EEF2, EFCAB4B, ELMOD2, EMP2, ERCC1, ERP44, EXOSC4, FADD, FPR2, GCNT3, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, IRF5, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LCP1, LFNG, LPCAT1, LYN, MAN2B1, MANBA, MFNG, MICB, MLEC, MSH2, MYO1C, NLRC5, NLRP3, NPC2, P2RX1, PA2G4, PAK1, PDAP1, PDXK, PGLYRP1, PIK3R2, PLAC8, PLCG2, PLEKHO2, POLR3B, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTK2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SBNO2, SCAMP1, SEMA4A, SERPINB1, SIGLEC5, SLAMF1, SLC2A3, STK10, SVIP, TIMP2, TMC6, TMEM179B, TOLLIP, TRIM11, TRIM25, TRPM2, TUBB, UBR4, VAMP2, VAV2, VAV3, VCP, WIF1, XRCC5, ZNF175

TABLE S5-continued

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)

# Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ	Genes
GO Biological Process	GO: 0016032	viral process	16	8.15E-07	1.05E-02	6.57E-04	LPCAT1, LYN, MAN2B1, MANBA, MICB, MLEC, MSH2, NPC2, P2RX1, PA2G4, PDAP1, PDXX, PGLYRP1, PLAC8, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SCAMP1, SERPINB1, SIGLEC5, SLAMF1, SLC2A3, STK10, SVIP, TMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VAMP2, VCP, XRCC5, ABI1, ACY3, ATF7IP, ATG7, ATP6V0C, ATP6V1G2-DDX39B, BIN1, BUB1, C9orf69, CCL1, CCNA2, CD46, CD81, CHD6, CHMP2A, CHMP5, CHMP6, CREBBP, CRTC2, CRTC3, CXADR, DAXX, DLG1, DPP4, DYRK1A, EIF3B, EIF3D, EIF3L, FADD, FBLN1, GTF2E1, H2AFX, HLA-B, HSPA8, HTATIP2, IL16, IPO5, ITGB1, ITGB7, KPNA2, KPNA4, KPNA7, LAMP1, LYN, MDFIC, MFGE8, MICB, MVBI2A, NFX1, NUCKS1, NUP210, NUP88, NUPL1, PABPN1, PCBP1, POLR2E, POM121, PSMB10, PTBP1, RAB11FIP4, RAB7A, RAE1, RPL18, RPL32, RPL7, RPLP1, RPS14, RPS25, RPS26, RPS29, RPS3A, SCARB1, SF3B2, SLAMF1, SP1, SPEN, TAF4, TBKBP1, TFRC, TGFB1, TNFRSF1A, TRIM25, UBC, UBR4, UNG, USP6NL, VCP, VPS18, VPS37A, VPS37C, VPS4B, WAPAL, XRCC5, ZYX
GO Biological Process	GO: 0044764	multi-organism cellular process	17	1.94E-06	2.50E-02	1.47E-03	ABI1, ACY3, ATF7IP, ATG7, ATP6V0C, ATP6V1G2-DDX39B, BIN1, BUB1, C9orf69, CCL1, CCNA2, CD46, CD81, CHD6, CHMP2A, CHMP5, CHMP6, CREBBP, CRTC2, CRTC3, CXADR, DAXX, DLG1, DPP4, DYRK1A, EIF3B, EIF3D, EIF3L, FADD, FBLN1, GTF2E1, H2AFX, HLA-B, HSPA8, HTATIP2, IL16, IPO5, ITGB1, ITGB7, KPNA2, KPNA4, KPNA7, LAMP1, LYN, MDFIC, MFGE8, MICB, MVBI2A, NFX1, NUCKS1, NUP210, NUP88, NUPL1, PABPN1, PCBP1, POLR2E, POM121, PSMB10, PTBP1, RAB11FIP4, RAB7A, RAE1, RPL18, RPL32, RPL7, RPLP1, RPS14, RPS25, RPS26, RPS29, RPS3A, SCARB1, SF3B2, SLAMF1, SP1, SPEN, TAF4, TBKBP1, TFRC, TGFB1, TNFRSF1A, TRIM25, UBC, UBR4, UNG, USP6NL, VCP, VPS18, VPS37A, VPS37C, VPS4B, WAPAL, XRCC5, ZYX
GO Biological Process	GO: 1904429	regulation of t-circle formation	18	2.86E-06	3.69E-02	2.05E-03	ERCC1, SLX1A, XRCC5
GO Biological Process	GO: 0045321	leukocyte activation	20	3.93E-06	5.08E-02	2.54E-03	ABL1, ADAM17, ADAM9, APAF1, APBB1IP, ATG7, ATP11B, ATP6V0C, B4GALT1, BCL3, BCL6, CAT, CCT8, CD300A, CD58, CD74, CD97, CHD7, CKAP4, CNN2, CORO1A, COTL1, CPNE3, CREG1, CRISPLD2, CRTC3, CTSZ, CXADR, CYLD, DHRS2, DLG1, DLL4, DNAJC13, DNAJC3, DOCK2, DPP4, EEF2, EFCAB4B, ERCC1, ERP44, FADD, FPR2, GDI2, GLI3, GON4L, HMHA1, HSP90AA1, HSPA8, ICOSLG, IL7, IMPDH1, ITGB1, ITGB2, KCMF1, KIF13B, KLF6,

TABLE S5-continued

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)							
#	Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ Genes
GO Biological Process	GO: 0044403	symbiosis, encompassing mutualism through parasitism	19	3.92E-06	5.05E-02	2.66E-03	LAIR1, LAMP1, LAMTOR2, LCP1, LFNG, LPCAT1, LYL1, LYN, MAN2B1, MANBA, MAPT, MFNG, MICB, MLEC, MSH2, MYH9, NDRG1, NPC2, ONECUT1, P2RX1, PA2G4, PDAP1, PDXK, PGLYRP1, PLAC8, PLCG2, PLEKHO2, POU1F1, PRCP, PRDX6, PREX1, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SBNO2, SCAMP1, SEMA4A, SERPINB1, SHH, SIGLEC5, SKAP2, SLAMF1, SLC2A3, SP3, SPI1, STK10, SVIP, TBX21, TGFB1, TIMP2, TMC6, TMEM179B, TNFSF4, TOLLIP, TRAF6, TRPM2, TUBB, TXLNA, UBR4, VAMP2, VCP, XRCC5, ZFP36L2
GO Biological Process	GO: 0044419	interspecies interaction between organisms	21	4.38E-06	5.65E-02	2.69E-03	AB11, ACY3, ATF7IP, ATG7, ATP6V0C, ATP6V1G2-DDX39B, BIN1, BUB1, C9orf69, CBLL1, CCL1, CCNA2, CD46, CD81, CFL1, CHD6, CHMP2A, CHMP5, CHMP6, CREBBP, CRTC2, CRTC3, CXADR, DAXX, DLG1, DPP4, DYRK1A, EIF3B, EIF3D, EIF3L, FADD, FBLN1, GTF2E1, H2AFX, HLA-B, HSPA8, HTATIP2, IL16, IPO5, ITGB1, ITGB7, KPNA2, KPNA4, KPNA7, LAMP1, LYN, MDFIC, MFGE8, MICB, MVB12A, NFX1, NUCKS1, NUP210, NUP88, NUPL1, PABPN1, PCBP1, PGLYRP1, POLR2E, POM121, PSMB10, PTBP1, RAB11FIP4, RAB7A, RAE1, RPL18, RPL32, RPL7, RPLP1, RPS14, RPS25, RPS26, RPS29, RPS3A, SCARB1, SF3B2, SLAMF1, SP1, SPEN, TAF4, TBKBP1, TFAP4, TFRC, TGFB1, TNFRSF1A, TRIM25, UBC, UBR4, UNG, USP6NL, VCP, VPS18, VPS37A, VPS37C, VPS4B, WAPAL, XRCC5, ZYX
GO Biological Process	GO: 2000767	positive regulation of cytoplasmic translation	23	5.80E-06	7.48E-02	3.25E-03	EEF2, METTL3, YTHDF2
GO Biological Process	GO: 0048524	positive regulation of viral process	22	5.80E-06	7.48E-02	3.40E-03	ADARB1, C9orf69, CD74, CFL1, CHMP2A, CNOT7, HSPA8, MDFIC, MVB12A, NELFCD, NR5A2, NUCKS1, PFN1, PKN2, POLR2D, POLR2E, RAB7A, SP1, STAU1, SUPT4H1, TFAP4, TMPRSS2, TRIM11, VPS4B
GO Biological Process	GO: 1904245	regulation of polynucleotide adenylyltransferase activity	24	6.80E-06	8.78E-02	3.66E-03	PABPN1, ZFP36

TABLE S5-continued

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)							
# Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ	Genes
GO Biological Process	GO:0036258	multivesicular body assembly	25	9.06E-06	1.17E-01	4.67E-03	CHMP2A, CHMP5, CHMP6, MVB12A, VPS25, VPS37A, VPS37C, VPS4B
GO Biological Process	GO:0019081	viral translation	26	9.62E-06	1.24E-01	4.77E-03	EIF3B, EIF3D, EIF3L, PTBP1
GO Biological Process	GO:0036257	multivesicular body organization	27	1.17E-05	1.50E-01	5.57E-03	CHMP2A, CHMP5, CHMP6, MVB12A, VPS25, VPS37A, VPS37C, VPS4B
GO Biological Process	GO:0044027	hypermethylation of CpG island	28	1.66E-05	2.14E-01	7.64E-03	GSK3A, SPI1
GO Biological Process	GO:0046755	viral budding	31	2.46E-05	3.17E-01	1.02E-02	CHMP2A, CHMP5, CHMP6, MVB12A, VPS25, VPS37A, VPS37C, VPS4B
GO Biological Process	GO:1904431	positive regulation of t-circle formation	29	2.32E-05	2.99E-01	1.03E-02	ERCC1, SLX1A
GO Biological Process	GO:0075522	IRES-dependent viral translational initiation	30	2.45E-05	3.16E-01	1.05E-02	EIF3B, EIF3D, PTBP1
GO Biological Process	GO:1901835	positive regulation of deadenylation-independent decapping of nuclear-transcribed mRNA	32	2.63E-05	3.39E-01	1.06E-02	ZFP36
GO Biological Process	GO:1904246	negative regulation of polynucleotide adenylyltransferase activity	32	2.63E-05	3.39E-01	1.06E-02	ZFP36
GO Biological Process	GO:0075525	viral translational termination-reinitiation	34	2.82E-05	3.64E-01	1.07E-02	EIF3B, EIF3D, EIF3L
GO Biological Process	GO:0045872	positive regulation of rhodopsin gene expression	35	2.93E-05	3.78E-01	1.08E-02	NRL
GO Biological Process	GO:0071348	cellular response to interleukin-11	36	3.43E-05	4.43E-01	1.23E-02	SBNO2
GO Biological Process	GO:1990314	cellular response to insulin-like growth factor stimulus	37	4.09E-05	5.28E-01	1.43E-02	CCNA2, CRK, GHSR, SLC25A33, TGFB1
GO Biological Process	GO:0019058	viral life cycle	41	5.60E-05	7.22E-01	1.76E-02	ATP6V1G2-DDX39B, CD46, CD81, CHMP2A, CHMP5, CHMP6, CXADR, DPP4, EIF3B, EIF3D, EIF3L, ITGB1, ITGB7, KPNA2, KPNA4, KPNA7, LAMP1, MVB12A, NUP210, NUP88, NUPL1, PCBPI, POM121, PTBP1, RAB7A, RAE1, RPL18, RPL32, RPL7, RPLP1, RPS14, RPS25, RPS26, RPS29, RPS3A, SCARB1, SLAMF1, TFRC, UBC, USP6NL, VCP, VPS18, VPS37A, VPS37C, VPS4B
GO Biological Process	GO:0019068	virion assembly	40	5.52E-05	7.12E-01	1.78E-02	CHMP2A, CHMP5, CHMP6, MVB12A, UBC, USP6NL, VPS37A, VPS37C, VPS4B
GO Biological Process	GO:0072367	regulation of lipid transport by regulation of	38	5.25E-05	6.77E-01	1.78E-02	NCOR1, PPARA, SREBF2

TABLE S5-continued

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)							
# Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ	Genes
GO Biological Process	GO:0061077	transcription from RNA polymerase II promoter chaperone-mediated protein folding	39	5.42E-05	6.99E-01	1.79E-02	BAG1, CALR, CCT5, CCT8, CD74, CHORDC1, DFFA, DNAJB12, DNAJB2, FKBP5, HSPA8, PDIA4
GO Biological Process	GO:0019262	N-acetylneuraminate catabolic process	42	5.98E-05	7.71E-01	1.84E-02	AMDHD2, NAGK, NPL
GO Biological Process	GO:1902251	negative regulation of erythrocyte apoptotic process	43	6.58E-05	8.48E-01	1.97E-02	EPO
GO Biological Process	GO:0002192	IRES-dependent translational initiation	44	7.04E-05	9.09E-01	2.07E-02	EIF3B, EIF3D, PTBP1
GO Biological Process	GO:0006283	transcription-coupled nucleotide-excision repair	45	8.01E-05	1.00E+00	2.30E-02	AQR, CCNH, COPS2, COPS3, COPS4, ERCC1, LIG1, LIG3, POLR2D, POLR2E, PRPF19, RFC3, UBC, XAB2
GO Biological Process	GO:0071233	cellular response to leucine exocytosis	46	8.20E-05	1.00E+00	2.30E-02	LARS, MTOR, RPTOR, RRAGD
GO Biological Process	GO:0006887		47	8.50E-05	1.00E+00	2.33E-02	ACTN4, APAF1, ARGEF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD109, CD300A, CD58, CD97, CHP1, CKAP4, CNN2, CORO1A, COTL1, CPNE3, CREG1, CRISPLD2, CTSW, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCAB4B, ENSG00000263620, ERP44, EXOC6B, EXOC7, FAM3C, FERMT3, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ISLR, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2, LLGL2, LPCAT1, LYN, MAN2B1, MANBA, MLEC, NKD2, NPC2, P2RX1, PA2G4, PAK1, PCDH7, PDAP1, PDXK, PGLYRP1, PIP5K1C, PLAC8, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAB8B, RAP2B, SCAMP1, SERPINB1, SIGLEC5, SLC2A3, SPP2, STK10, STXBP5, SVIP, SYNGR3, SYNJ1, SYT1, SYT10, SYT11, SYT13, TGFB1, TGFB3, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, TXLNA, UBR4, VAMP2, VCP, VMP1, VPS18, VPS45, XRCC5
GO Biological Process	GO:0030421	defecation	48	1.02E-04	1.00E+00	2.75E-02	MDK
GO Biological Process	GO:0050434	positive regulation of viral transcription	49	1.07E-04	1.00E+00	2.82E-02	MDFIC, NELFCD, NUCKS1, PFN1, POLR2D, POLR2E, SP1, SUPT4H1, TFAP4
GO Biological Process	GO:0002921	negative regulation of humoral immune response	50	1.11E-04	1.00E+00	2.87E-02	CD46, FOXJ1, PTPN6, SPINK5
GO Biological Process	GO:0016197	endosomal transport	51	1.24E-04	1.00E+00	3.14E-02	ANKRD27, ANKRD50, ARL4C, C9orf72, CHMP2A, CHMP5, CHMP6, CORO1A, DENND3, DNML1, EMP2, FAM109A, HOOK1, HOOK2, LAPT4B, MGRN1, MVB12A, PICALM, RAB10, RAB17, RAB7A, SGSM2, SNX18, SNX5,

TABLE S5-continued

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)

# Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ	Genes
GO Biological Process	GO: 0032509	endosome transport via multivesicular body sorting pathway	52	1.27E-04	1.00E+00	3.16E-02	SNX8, SORT1, SPAG9, STX10, TINAGL1, UBC, USP6NL, VCP, VPS13A, VPS18, VPS25, VPS35, VPS37A, VPS37C, VPS39, VPS4B, VPS53, WDR81, WIP11
GO Biological Process	GO: 1905154	negative regulation of membrane invagination	53	1.39E-04	1.00E+00	3.37E-02	CD300A, SYT11
GO Biological Process	GO: 0061395	positive regulation of transcription from RNA polymerase II promoter in response to arsenic-containing substance	54	1.57E-04	1.00E+00	3.76E-02	ATF4
GO Biological Process	GO: 0030393	fructoselysine metabolic process	56	1.67E-04	1.00E+00	3.85E-02	FN3K
GO Biological Process	GO: 0006396	RNA processing	57	1.71E-04	1.00E+00	3.86E-02	AAR2, AARS2, ABT1, ADARB1, APOBEC2, AQR, ATP6V1G2-DDX39B, BUD31, CACTIN, CCNH, CCNL1, CDC5L, CELF2, CHD7, CIR1, CIRH1A, CPSF2, CPSF3, CPSF6, CSNK1E, CTU2, CW22, DDX19A, DDX39A, DEDD2, DHX35, DIEXF, DUS2, ERN1, ESRP2, EXOSC4, EXOSC9, GPATCH1, HNRNPF, HSPA8, INTS10, INTS3, KIAA1429, KIAA1456, KRI1, LSM7, MAPKBP1, MBNL1, MDN1, METTL16, METTL3, MPHOSPH6, NAT10, NOL11, NOP10, NOVA1, NSRP1, NWD1, PA2G4, PABPN1, PAPD5, PAPOLG, PCBP1, POLDIP3, POLR2D, POLR2E, PPP1R9B, PRKACA, PRMT7, PRPF19, PTBP1, PTBP2, PTBP3, PTCD2, RAVER2, RBMS1, RPL18, RPL32, RPL7, RPLP1, RPP21, RPP38, RPS14, RPS25, RPS26, RPS29, RPS3A, RRP1, SARNP, SCAF8, SF3A2, SF3A3, SF3B1, SF3B2, SLBP, SMU1, SNRNP70, SNRPE, SPEN, SRRM2, SRSF1, SRSF2, SUGP2, SUPT4H1, SYMPK, TARBP1, TFB1M, THUMPD2, TSN, U2AF2, UTP3, WDR4, XAB2, XRN2, YBEY, ZNF473, ZRANB2
GO Biological Process	GO: 0016072	rRNA metabolic process	55	1.67E-04	1.00E+00	3.91E-02	ABT1, CHD7, CIRH1A, CSNK1E, DEDD2, DIEXF, EXOSC4, EXOSC9, KRI1, MDN1, METTL16, MPHOSPH6, NAT10, NOL11, NOP10, PA2G4, PAPD5, RPL18, RPL32, RPL7, RPLP1, RPP21, RPP38, RPS14, RPS25, RPS26, RPS29, RPS3A, RRP1, TARBP1, TFB1M, UTP3, XRN2, YBEY
GO Biological Process	GO: 0045055	regulated exocytosis	58	1.86E-04	1.00E+00	4.14E-02	ACTN4, APAF1, ATG7, ATP11B, ATP6V0C, B4GALT1, CAT, CCT8, CD109, CD300A, CD58, CD97, CHP1, CKAP4, CNN2, CORO1A, COTL1, CPNE3, CREG1, CRISPLD2, CTSW, CTSZ, DNAJC13, DNAJC3, DOCK2, EEF2, EFCA4B, ERP44, FAM3C, FERMT3, FPR2, GDI2, HMHA1, HSP90AA1, HSPA8, IMPDH1, ISLR, ITGB2, KCMF1, LAIR1, LAMP1, LAMTOR2,

TABLE S5-continued

Table S5: GO enrichment for class I hotspots (HCC vs. Healthy)							
# Ontology	ID	Desc	BinomRank	BinomP	BinomBonfP	BinomFdrQ	Genes
GO Biological Process	GO: 0031124	mRNA 3'-end processing	59	1.96E-04	1.00E+00	4.28E-02	LPCAT1, LYN, MAN2B1, MANBA, MLEC, NPC2, P2RX1, PA2G4, PCDH7, PDAP1, PDXK, PGLYRP1, PIP5K1C, PLAC8, PLEKHO2, PRCP, PRDX6, PRG3, PSAP, PSMD1, PSMD3, PSMD6, PTGES2, PTPN6, PTPRN2, PYGB, QPCT, RAB10, RAB4B, RAB7A, RAP2B, SCAMP1, SERPINB1, SIGLEC5, SLC2A3, SPP2, STK10, SVIP, SYNGR3, SYNJ1, SYT1, SYT10, SYT11, SYT13, TGFB1, TGFB3, TIMP2, TMC6, TMEM179B, TOLLIP, TRPM2, TUBB, UBR4, VAMP2, VCP, XRCC5
GO Biological Process	GO: 0033108	mitochondria I respiratory chain complex assembly	60	2.30E-04	1.00E+00	4.94E-02	AARS2, ATP5SL, C11orf83, C6orf57, COA5, COX19, NDUFA6, NDUFAB1, NDUFAF1, NDUFB1, NDUFB7, NDUFC1, NDUFV2, OXA1L, PET100, SLC25A33

[0118] Overall, in early-stage cancer patients, we found the increases in fragmentation levels at hotspots near micro-satellites (Class II hotspots) and the decreases in fragmentation levels at hotspots near CTCF and promoters (Class I hotspots), which are enriched in the immune-related GO terms from the peripheral immune cells.

Cell-Free DNA Fragmentation Hotspots can Mitigate the Overdiagnosis Concern.

[0119] Overdiagnosis is one of the major concerns for the diagnosis of early-stage cancer. We next explored whether or not the IFS signals from cfDNA fragmentation hotspots could also characterize the differences between early-stage HCC and non-malignant liver diseases. We identified the hotspots on the additional cfDNA WGS datasets from 67 patients with chronic HBV infection and 36 patients with HBV-associated liver cirrhosis in the same study[25]. PCA analysis of IFS signals across all the hotspots suggested a clear separation between early-stage HCC and non-malignant liver diseases, as well as healthy controls (FIG. S12a). To test if the separation of samples is due to the possible

batch effect, we performed PCA on IFS from matched random genomic regions in the same sample and did not observe a clear separation between groups of samples (FIG. S12b). Another possible technical artifact for the clear separation between HCC and other conditions could be due to our pooling strategy for the hotspot calling in low-coverage WGS data. The hotspot calling on the pooled group may enrich the regions with similar depletions in the genome without any meaningful biological indications. To test if the separation of samples is due to this artifact, we randomly grouped the samples and called the hotspots from these random groups with the matched group sizes. The PCA results did not show any separations as expected (FIG. S12c). We further selected the top 30,000 most variable hotspots, performed the unsupervised hierarchical clustering, and observed the clear dynamics of the fragmentation patterns among early-stage HCC, HBV, Cirrhosis, and healthy controls (FIGS. S13-14). Finally, by 10-fold cross-validation, the linear SVM model showed a higher classification performance (83% sensitivity at 100% specificity) than other methods from the same dataset (FIG. S15, Table S6-7).

TABLE S6

Performance comparison in HCC vs. HBV + Cirrhosis (before GC bias correction)						
		AUC	Sensitivity @100% specificity	Sensitivity @98% specificity	Sensitivity @95% specificity	Sensitivity @85% specificity
IFS hotspots	0.9770 (0.95 CI: 0.9533 (0.959588-0.9951))	CI: 0.6670-0.9997)	0.8333 (0.95 CI: 0.6670-0.9997)	0.8333 (0.95 CI: 0.6670-0.9997)	0.8333 (0.95 CI: 0.6670-0.9997)	0.9556 (0.95 CI: 0.9074-1.0000)
CNV	0.7400 (0.95 CI: 0.5333 (0.95 0.7025-0.7775))	CI: 0.4127-0.6539)	0.6222 (0.95 CI: 0.5173-0.7272)	0.6222 (0.95 CI: 0.5173-0.7272)	0.6222 (0.95 CI: 0.5173-0.7272)	0.7611 (0.95 CI: 0.6474-0.8748)
mtDNA	0.9414	0.1556	0.6556	0.6556	0.7556	0.8444

TABLE S7

Performance in HCC vs. HBV + Cirrhosis (after GC bias correction)				
AUC	Sensitivity @100% specificity	Sensitivity @98% specificity	Sensitivity @95% specificity	Sensitivity @85% specificity
IFS hotspots 0.9772 (0.95 CI: 0.9111 (0.95 0.9111 (0.95 0.9111 (0.95 0.9333 (0.95 hotspots 0.9603-0.9940) CI: 0.8676- 0.9547) CI: 0.8676- 0.9547) CI: 0.8676- 0.9547) 0.9547)				

Cell-Free DNA Fragmentation Hotspots Boost the Power for the Detection and Localization of Multiple Early-Stage Cancers.

[0120] One of the biggest challenges for the detection of early-stage cancer is to obtain high accuracy across multiple types of cancer, which is not available in clinics yet. To further validate our method in a more comprehensive early-stage cancer dataset, we collected publicly available low-coverage cfDNA WGS data (~1x/sample) from 208 patients across seven different kinds of cancer (88% in stage I-III, colon, breast, lung, gastric, bile duct, ovary, and pancreatic cancer) and matched 215 healthy controls in the same study[4]. We applied a similar strategy to the HCC study above for the hotspot calling (pool the samples to achieve enough coverage as stated in FIG. S7). Across seven different types of cancer and healthy conditions, the z-score of IFS signals in the most variable fragmentation hotspots showed clear cancer-specific fragmentation patterns in both t-SNE visualization and unsupervised hierarchical clustering (FIG. 4a-b, FIG. S16, Details in Supplementary Methods). The fragmentation patterns alone at these hotspots can separate the cancer types very well. By 10-fold cross-validation, the linear SVM model showed a consistent high classification performance across different stages for its high sensitivity at high specificity (64% sensitivity to 82% sensitivity at 100% specificity). Overall, the performance is complementary with large-scale fragmentation patterns and significantly higher in different stages than previously reported results by CNVs and mtDNA from the same dataset[4] (FIG. 4c, Table 1). For example, at 100% specificity, we achieved 93% sensitivity (95% CI: 85%-100%) in gastric cancer, 88% sensitivity (95% CI: 76%-100%) in colorectal cancer, and 81% sensitivity (95% CI: 76%-91%) in breast cancer, which of these are poorly detected at high specificity level by other liquid biopsy studies[4,29-32]. (FIG. S17-18, Table 1, Table S8). In the other cancer types, the performance is largely comparable to the previous results[4]. We also tested the performance before GC bias correction, and the results are largely the same (FIG. S17). Moreover, we estimated the tumor fractions in each sample by CNV based approach (ichorCNA)[33]. Our approach showed high performance

even with a tumor fraction of less than 2%, and the performance is robust across samples with different tumor fractions (FIG. S19).

TABLE 1

CRAG Performance for the Detection of Early Stage Cancers.						
100% specificity						
		Individ- uals analysed	Indi- viduals detected	Sensi- tivity (%)	95%	
Cancer Type	Breast	54	44	0.8133	0.7168-0.9098	
	Bile duct	26	11	0.4167	0.1819-0.6515	
	Colorectal	27	24	0.8833	0.7635-1.0000	
	Gastric	27	25	0.9333	0.8462-1.0000	
	Lung	12	6	0.5000	0.2078-0.7922	
	Ovarian	28	15	0.5500	0.3519-0.7451	
	Pancreatic	34	19	0.5667	0.4251-0.7082	
Cancer Stage	I	41	28	0.6350	0.4428-0.8272	
	II	109	72	0.6667	0.5816-0.7518	
	III	33	25	0.8200	0.6813-0.9587	
	I-IV	205	141	0.6858	0.6098-0.7617	
95% specificity						
		Indi- viduals detected	Sensi- tivity (%)	95% CI (%)	Indi- viduals detected	Sensi- tivity (%)
	48	0.8867	0.7892-0.9842		51	0.9433
	12	0.4500	0.2320-0.6680		14	0.5333
	25	0.9162	0.8051-1.0000		25	0.9167
	25	0.9333	0.8462-1.0000		26	0.9667
	8	0.6500	0.3560-0.9400		8	0.6500
	23	0.8167	0.6692-0.9741		24	0.8500
	21	0.6333	0.4790-0.7877		22	0.6583
	34	0.8290	0.7046-0.9454		34	0.8250
	79	0.7297	0.6603-0.8092		85	②
	28	0.8892	0.7796-0.9904		30	0.9360
	169	0.7742	0.7229-0.8255		167	②
85% specificity						

② indicates text missing or illegible when filed

TABLE S8

Performance in seven types of cancer vs. healthy samples (before GC bias correction)				
AUC	Sensitivity @100% specificity	Sensitivity @98% specificity	Sensitivity @95% specificity	Sensitivity @85% specificity
Breast cancer vs. healthy 0.9887 (95 CI: 0.9771- 1.0000) 0.8900 (95 CI: 0.7936- 1.0000) 0.8900 (95 CI: 0.7936- 1.0000) 0.9267 (95 CI: 0.8436- 1.0000) 1.0000 (95 CI: 1.0000- 1.0000)				

TABLE S8-continued

Performance in seven types of cancer vs. healthy samples (before GC bias correction)					
	AUC	Sensitivity @100% specificity	Sensitivity @98% specificity	Sensitivity @95% specificity	Sensitivity @85% specificity
Bile duct vs. healthy	0.7556 (95 CI: 0.6651- 0.8460)	0.3167 (95 CI: 0.1075- 0.5258)	0.3167 (95 CI: 0.1075- 0.5258)	0.4333 (95 CI: 0.2200- 0.6467)	0.4667 (95 CI: 0.2731- 0.6602)
Colorectal vs. healthy	0.9890 (95 CI: 0.9736- 1.0000)	0.9000 (95 CI: 0.8002- 0.9998)	0.9000 (95 CI: 0.8002- 0.9998)	0.9667 (95 CI: 0.9013- 1.0000)	0.9667 (95 CI: 0.9013- 1.0000)
Gastric vs. healthy	0.9271 (95 CI: 0.8428- 1.0000)	0.7833 (95 CI: 0.6290- 0.9377)	0.7833 (95 CI: 0.6290- 0.9377)	0.8167 (95 CI: 0.6592- 0.9471)	0.8167 (95 CI: 0.6592- 0.9471)
Lung vs. healthy	0.9019 (95 CI: 0.8382- 0.9657)	0.3500 (95 CI: 0.0560- 0.6440)	0.3500 (95 CI: 0.0560- 0.6440)	0.5000 (95 CI: 0.2078- 0.7922)	0.8000 (95 CI: 0.5833- 1.0000)
Ovarian vs. healthy	0.9718 (95 CI: 0.9418- 1.0000)	0.7833 (95 CI: 0.6290- 0.9377)	0.7833 (95 CI: 0.6290- 0.9377)	0.8833 (95 CI: 0.7636- 1.0000)	0.9667 (95 CI: 0.9013- 1.0000)
Pancreatic vs. healthy	0.8188 (95 CI: 0.7214- 0.9163)	0.5500 (95 CI: 0.4055- 0.6945)	0.5500 (95 CI: 0.4055- 0.6945)	0.5750 (95 CI: 0.4451- 0.7049)	0.6583 (95 CI: 0.4889- 0.8278)

[0121] Another big challenge for the diagnosis of early-stage cancer is identifying the cancer types for the most appropriate follow-up treatment choices. Here, we asked whether we can identify the tissues-of-origin of cancer samples by using the fragmentation levels alone. In the cancer positive samples identified above by machine learning algorithm, without any clinical information about the patients, we further localized the sources of cancer to one or two anatomic sites in a median of 85% of these patients across five different cancer types and 82.5% accuracy across six different cancer types. Furthermore, we were able to localize the source of the positive test to a single organ in a median of 65% of these patients across five different cancer types and 56% accuracy across six different cancer types. Our performance is similar to the previous reports using the combination of mutations and proteins[29] or DNA methylation[30] but superior to any other fragmentation approach (FIG. 4d, Table S9, FIG. S20) (Details in Methods). The prediction accuracy varies among tumor types, from 70% (95% CI: 44%-96%) in ovarian cancer to 98% (95% CI: 94%-100%) in breast cancer (FIG. 4d and Table S9), but significantly higher than random choices by the sample frequency in each cancer type (FIG. S21).

TABLE S9

Performance in multi-cancer classification (after GC bias correction)			
Cancer type	Number of individuals	Top 1 accuracy	Top 2 accuracy
Breast cancer	44	0.6550 (95 CI: 0.4800- 0.8300)	0.9800 (95 CI: 0.9408- 1.0000)
Colorectal cancer	24	0.6833 (95 CI: 0.4742- 0.8925)	0.7833 (95 CI: 0.6290- 0.9377)
Gastric cancer	25	0.5333 (95 CI: 0.2958- 0.7709)	0.8667 (95 CI: 0.7307- 1.0000)
Ovarian cancer	15	0.4000 (95 CI: 0.1152- 0.6848)	0.7000 (95 CI: 0.4387- 0.9613)
Pancreatic cancer	19	0.6500 (95 CI: 0.4408- 0.8592)	0.8500 (95 CI: 0.6408- 1.0000)
Breast cancer	44	0.5500 (95 CI: 0.4084- 0.6916)	0.9550 (95 CI: 0.8957- 1.0000)

TABLE S9-continued

Performance in multi-cancer classification (after GC bias correction)			
Cancer type	Number of individuals	Top 1 accuracy	Top 2 accuracy
Colorectal cancer	24	0.5667 (95 CI: 0.3589- 0.7744)	0.7833 (95 CI: 0.6368- 0.9298)
Gastric cancer	25	0.6500 (95 CI: 0.4298- 0.8702)	0.8667 (95 CI: 0.7307- 1.0000)
Ovarian cancer	15	0.3000 (95 CI: 0.0387- 0.5613)	0.6550 (95 CI: 0.3560- 0.9440)
Pancreatic cancer	19	0.8500 (95 CI: 0.6408- 1.0000)	0.9000 (95 CI: 0.7693- 1.0000)
Bile duct cancer	11	0.2000 (95 CI: 0.0000- 0.4613)	0.4000 (95 CI: 0.0799- 0.7201)

Discussion

[0122] In summary, the current disclosure provides a computational approach, named CRAG, to de novo identify the cfDNA fragmentation hotspots by weighting fragment coverages with the size information. Similar to the previous studies on the open chromatin regions within the cells, cfDNA fragmentation hotspots are highly enriched at known gene-regulatory elements. The in vivo fragmentation process, however, is complicated. A previous study suggested the co-existence of fragmentation coldspots and nucleosome protection but did not characterize the fragmentation hotspots, due to some computational challenges[3]. Genomic regions with a higher fragmentation rate do not always indicate the open chromatin regions. Besides nucleosomes, both biological issues (e.g., DNA methylation and histone modifications)[2,27] and technical artifacts (e.g., G+C %, k-mer, and mappability)[34,35] can affect the measurements of fragmentation level. After excluding the known effects of open chromatin regions and technical artifacts, our genome-wide analysis here revealed the enrichment of hotspots after the 3' end of transposable elements and potentially associated with local DNA methylation level, which suggested the unknown origin of the cfDNA fragmentation processes.

[0123] Further, in early-stage cancer, we found the increases in fragmentation levels at the hotspots near microsatellites and the DNA methylation aberrations from another

dataset at the same regions, which indicated the importance of exploring the fragmentation aberrations at the de novo characterized regions. More importantly, the hypo-fragmented hotspots in early-stage cancer are mostly located at promoters of genes enriched in the immune-related GO terms from the peripheral immune cells. Many recent efforts on the detection of early-stage cancer, however, focused on how to enrich the circulating tumor DNA signals from tumor cells[29,32], which ignored the critical role of peripheral immune aberrations during the cancer initiations[36]. In addition, the CTCF motif is highly enriched at these hypo-fragmented hotspots, which indicates the potential three-dimensional chromatin organization changes during the initiation of early-stage cancer, which has been reported before but not characterized by the cfDNA approaches[37]. Overall, our results suggested that the de novo characterization of fine-scale cfDNA fragmentation hotspots is critical to reveal the unknown gene-regulatory aberrations in pathological conditions.

[0124] Previous efforts had been made to characterize the nucleosome-free regions by using the depletion of coverages from MNase-seq/ChIP-seq assay[38]. The measurement of cfDNA fragmentation here, however, involves information from both fragment coverages and sizes. CRAG can be further improved by better integrating the fragment coverages and sizes, or even with more dimensions, such as the fragment orientation, jagged ends, and endpoint, to fully capture the spectrum of fragmentation. Also, G+C % bias is known to affect the peak calling result in ChIP-seq/ATAC-seq[39]. A better statistical model with the incorporation of GC normalization on both of the fragment coverages and sizes will improve our method's performance. PCR-free library preparation for WGS will also mitigate the concerns of GC bias and other sequencing artifacts[40].

[0125] For the detection and localization of early-stage cancer, we also identify several areas for further development. First, due to the limited availability of public cfDNA WGS datasets from early-stage cancer patients, the classification performance here is evaluated by multi-fold cross-validation on a relatively small sample-size cohort in each cancer type, similar to other cfDNA WGS studies[4]. Multiple independent large-scale prospective cohorts with similar cancer types will be a better way to assess the power of our approach for the diagnosis of early-stage cancer. Second, we pooled the low-coverage WGS samples from the same condition for the hotspot calling, which may cause the problem with a small number of samples. Due to the random drop out of the fragment coverages and many genomic windows in the genome, the number of falsely discovered hotspots without any biological interpretations will increase. Our current strategy by filtering low mappability regions and correcting GC bias is helpful to reduce the false positive rate for the hotspot detection. However, the accuracy of IFS signals at individual hotspots from each sample are still affected by the low-coverage data. Recent effort showed the possibility to integrate genome-wide mutational patterns at low-coverage WGS to enable the ultra-sensitive detection of cancer samples with limited cfDNA abundance[41], which is similar to our strategy for the IFS signals here. Since we narrow down the regions of interest, even with missing values at part of the loci, many other hotspots from the same sample will still provide informative signals rather than noises for the model to make the classifications. In the future, appropriate statistical models for the imputation of

missing fragmentation patterns may be useful to mitigate the missing data problem. Third, the proportion of cancer types and the ratio between cancer and healthy is not an unbiased representation of the average-risk population in the US. The sensitivity and specificity here may not represent the actual performance in the large-scale screening. Fourth, the proof-of-concept study on HCC here suggested the distinguished cfDNA fragmentation patterns between early-stage cancer and non-malignant liver disease controls. More cfDNA studies on non-malignant cancer, diseases, and benign status may be performed to minimize the overdiagnosis in the population-level screening. Lastly, in some cancer types, our fine-scale study here showed complementary classification performance compared with that in the previous large-scale fragmentation study at the same dataset[4]. For example, our results on gastric, breast, and colorectal cancer outperformed previous large-scale fragmentation studies, while at bile duct and lung cancer, the performance is reversed. Future combinations of the fragmentation patterns at multi-scales and information from other modalities or clinical meta-data may further improve the performance.

[0126] Our study here lays the foundation to non-invasively detect multiple early-stage cancers simultaneously on an existing matured high-throughput platform in a cost-effective way. It also paves the road to further elucidate the unknown gene-regulatory mechanisms in pathological conditions through the cfDNA fragmentation hotspots.

Materials and Methods

Public Datasets.

[0127] Public datasets used in this study were listed in Table S1.

Preprocess of Whole-Genome Sequencing Data.

[0128] The adapter was trimmed by Trimmomatic (v0.36) [42] in paired-end mode with the following parameters: ILLUMINACLIP:TruSeq3-PE.fa:2:30:10:2:keepBothReads MINLEN:36. After adapter trimming, reads were aligned to the human genome (GRCh37, human_glk_v37.fa) using BWA-MEM 0.7.15[43] with default parameters. PCR-duplicate fragments were removed by samblaster (v0.1.24) [44]. Only high-quality autosomal reads were used for all downstream analyses (both ends uniquely mapped, either end with mapping quality score of 30 or greater, properly paired, and not a PCR duplicate).

Preprocess of Whole-Genome Bisulfite Sequencing Data.

[0129] DNA methylation levels measured by WGBS in cfDNA from HCC patients and healthy individuals were obtained from previous publications (Details in Table S1) [28,45]. Single-end WGBS from cfDNA was processed by the following internal pipeline. Based on FastQC results on the distribution of four nucleotides along the sequencing cycle, the adapter was trimmed by Trim Galore! (v0.6.0) with cutadapt (v2.1.0) and with parameters “--clip_R1 10” and “--clip_R1 10 --three_prime_clip_R1 13”. After the adapter trimming, reads were aligned to the human genome (GRCh37, human_glk_v37.fa) by Biscuit (v0.3.10.20190402) with default parameters. PCR-duplicate reads were marked by samtools (v1.9)[46]. Only high-quality reads were used for all the downstream analyses (uniquely mapped, mapping quality score of 30 or greater, and not a

PCR duplicate). Methylation level at each CpG was called by Bis-SNP with default parameters in bissnp_easy_usage.pl[47].

Identification of cfDNA Fragmentation Hotspots by CRAG. [0130] Fragment coverages and sizes are both essential parts of the cfDNA fragmentation patterns. However, popular peak calling tools, such as MACS2[48], cannot address the signals from two different dimensions. Thus, we created an integrated fragmentation score (IFS) by weighting the fragment coverage based on the ratio of average fragment size in the window versus that in the whole chromosome. Specifically, we utilized a 200 bp sliding window with a 20 bp step to scan each chromosome (autosome only). In the i_{th} window:

$$IFS_i = n_i * \left(1 + \frac{l_i}{L}\right) \quad (\text{Eq. 1})$$

$$C_i = \lfloor IFS_i \rfloor \quad (\text{Eq. 2})$$

where C_i is the IFS score round down to the nearest integer in the i_{th} window, n_i is the number of fragments whose mid-points are located within the i_{th} window, l_i is the average fragment size in the i_{th} window, L is the average fragment size in the whole chromosome. Windows overlapped with dark regions or with average mappability scores smaller than 0.9 were removed. Dark regions were defined by the merged DAC blacklist and Duke Excluded from the UCSC table browser. Mappability score was generated by the GEM mappability program on the human reference genome (GRCh37, human_glk_v37.fa, 51mer)[49]. We assumed the background C_i following the negative binomial (NB) distribution.

$$C_i \sim NB(n, p) \quad (\text{Eq. 3})$$

[0131] We denoted the sample mean and sample variance as u and v . Thus, we can estimate NB parameters as follows:

$$p = \frac{\mu}{v} \quad (\text{Eq. 4})$$

$$n = \frac{\mu^2}{v} \frac{1}{1-p} \quad (\text{Eq. 5})$$

[0132] We utilize the NB model to test whether the C_i in the i_{th} window was significantly smaller than the local background (20 kb and 40 kb) and global background (the whole chromosome). In R, we can calculate p-values using the following function:

$$pnbinom(q, prob = p, size = n) \quad (\text{Eq. 6})$$

[0133] Only windows with a p-value smaller than a cut-off (p-value $\leq 1.0e-05$) in both the local and global background were kept for further analysis. P-value from the comparison with the global background was utilized for the multiple hypothesis corrections (Benjamini and Hochberg method). Windows with a false discovery rate (FDR) of more than

0.25 were filtered. Finally, significant windows with a distance of less than 200 bp to each other were merged as the final hotspots.

[0134] To remove the possible sequence composition bias caused by G+C % content, similar as previous study[4], locally weighted smoothing linear regression (loess, span=0.75) was utilized to regress out the GC covariates from the raw IFS score in each window. The mean IFS score in each chromosome was added back to the residual value after the correction. The hotspots were called based on the corrected IFS finally.

[0135] To check the possible fragmentation bias caused by k-mer, we first calculated the expected IFS by using the average IFS at each possible type of dimer (16 types) across the genome. Then at each location, the adjusted IFS was calculated by dividing the original IFS with the expected IFS based on the dimer composition at that location. Finally, the adjusted IFS at each location was multiplied by the ratios between the average adjusted IFS and average expected IFS in the same chromosome.

Benchmark the Accuracy to Predict the Open Chromatin Regions.

[0136] To benchmark the performance of our method on the open chromatin region calling, we utilized the 15-states chromHMM segmentation result across different cell types from NIH Epigenome Roadmap Consortium. We generated a balanced fragmentation-positive and fragmentation-negative group randomly sampled from two types of regions: (1) constitutively open regions: we used the -150 bp to 50 bp regions around the transcription starting sites which are overlapped with TssA chromHMM states shared across all cell types; (2) constitutively closed regions: we used the Quies chromHMM states shared across all cell types, then we randomly sampled the intervals from these regions with matched GC content and mappability as the constitutively open regions. We utilized the IFS score and k-mer ($k=2$) composition within these two types of regions as the features and applied the linear SVM with default parameters in the ten-fold cross-validation.

Cancer Early Detection by cfDNA Fragmentation Hotspots.

[0137] Here, we took the classification of liver cancer vs. healthy controls as an example. Ten-fold cross-validation was applied to evaluate the performance. At the training data set, all the liver cancer samples and healthy samples were pooled to identify the hotspots, respectively. We kept the top 30,000 most stable hotspots (ranked by the sum of variances in cancer and control group) as the feature for the classification. It is well known that the sequencing depths will largely affect the number of peaks called in ChIP-seq and ATAC-seq[19]. In Cristiano et al. dataset[4], the sample size in the healthy group is ten times larger than that in any cancer type, which will lead to the uneven sequencing depths between healthy controls and cancers. Thus, by following the similar procedures in the previous publication [19], we downsampled the number of healthy controls to the same size as cancer before hotspot calling in each comparison (e.g., Breast cancer vs. Healthy). IFS before and after GC bias correction have both been tested. IFS after GC bias correction was shown in the main figure for the classification. Only genomic regions at ± 100 bp of the hotspot center were used to retrieve the IFS in each sample (the same strategy was used in PCA and unsupervised clustering analysis). The IFS at each corresponding hotspot was

z-score transformed based on the mean and standard deviation at each chromosome of each sample. Finally, a support vector machine (SVM) classifier with linear kernel and default parameters (fitcsvm function at Matlab 2019b) was applied. At the testing dataset, the z-score transformed IFS in each sample was calculated at the hotspot regions identified from the training set in that particular fold. The average AUC and 95% Confidence Interval (95% CI) of the AUC was calculated based on the classification results at the testing dataset across the ten folds. To avoid the randomness of the data split, we repeated the cross-validation randomly ten times.

Tissues-of-Origin Predictions by cfDNA Fragmentation Hotspots.

[0138] Only samples predicted as cancer were kept for the tissues-of-origin analysis. The saturation analysis of the fragment number needed for hotspot calling suggested that 400 million fragments are required to achieve the saturated performance (FIG. S7, Details in Supplementary Methods). Thus, pathological conditions with less than 400 million fragments in total were not used for the tissues-of-origin analysis (e.g., lung cancer). Bile duct cancer was at the boundary condition with 380 million fragments. Therefore, we performed the analysis with or without bile duct cancer. By 10-fold cross-validation, similar to that in the cancer early detection part, hotspots for each cancer type in the training set were identified. The z-score transformed IFS after GC bias correction in each sample was obtained as the feature. Since the total number of fragments in breast cancer is much larger than that in the other cancer types, we downsampled breast cancer to the median sample size across all the cancer types. The centroid in each cancer type was then calculated by the z-score transformed IFS across all the hotspots in the training set. In the testing dataset, each sample was assigned to the top two candidate cancers based on their distance to the centroids in each cancer type identified at the training set. The distance was calculated by corr function with ‘Type’ of ‘Spearman’ at Matlab 2019b. To further narrow down the best candidate cancer type, decision tree models (fitctree function at Matlab 2019b) were learned to identify the better candidate by the top 100,000 most stable hotspots in each possible pair of cancer types at the training set. Finally, we applied the corresponding decision tree model on the top two candidates to further characterize the best candidate at the testing set.

Supplementary Methods

The Saturation Analysis of the Fragment Number Needed for the Hotspot Calling of cfDNA Fragmentation Hotspots.

[0139] A group of fragmentation-positive regions and fragmentation-negative regions were generated for the benchmark. For fragmentation-positive regions, we chose the CGI TSS that are overlapped with conserved TssA chromHMM states (15-state chromHMM) shared across the cell types from NIH Epigenome Roadmap. Regions that are -50 bp to +150 bp around these active TSS were defined as the fragmentation-positive regions. For fragmentation-negative regions, we chose the same number of random genomic regions from conserved Quies chromHMM states shared across the cell types but with the same chromosome, region size, G+C % content, and mappability score as that in fragmentation-positive regions.

[0140] We downsampled the high-quality fragments in the BH01 dataset from 1.2 billion to 10 million. We identified

the hotspots at these downsampled datasets and calculated TP (true positive), FP (false positive), TN (true negative), FN (false negative) based on their overlaps with the benchmark regions generated above. F-score was calculated:

$$Fscore = 2 * \frac{\text{Precision} * \text{Recall}}{\text{Precision} + \text{Recall}} \quad (\text{Eq. S1})$$

in which, Precision and Recall were calculated using equation (S2) and equation (S3), respectively:

$$\text{Precision} = \frac{TP}{TP + FP} \quad (\text{Eq. S2})$$

$$\text{Recall} = \frac{TP}{TP + FN} \quad (\text{Eq. S3})$$

[0141] The performance is saturated at ~0.9 F1-score with 400 million fragments. Even with 200 million fragments, we can still achieve good performance (~0.8 F1-score) (FIG. S7).

The Enrichment Analysis of the cfDNA Fragmentation Hotspots in Gene-Regulatory Elements.

[0142] The number of hotspots that overlapped with the regulatory element was counted by bedtools v2 [50]. After filtering out the dark regions and low mappability regions (mappability less than 0.9), random genomic regions were generated with matched chromosomes and sizes. Fisher exact test (two-tail) was performed to calculate the enrichment of hotspots over the matched random regions.

The Principal Component Analysis of the cfDNA Fragmentation Hotspots Across Different Diseases.

[0143] The cfDNA fragmentation hotspots were called at each pathological condition as described in the Methods. Principal Component Analysis (PCA) was performed on the z-score transformed IFS across all the fragmentation hotspots (pca function at Matlab 2019b).

Unsupervised Hierarchical Clustering Analysis of the cfDNA Fragmentation Hotspots Across Different Diseases.

[0144] The cfDNA fragmentation hotspots were called at each pathological condition as described in the Methods. Top N most variable hotspots were kept for the clustering (ranked by the variation across all the samples). Spearman’s rank correlation was utilized to evaluate the distance among the samples. Also, weighted average distance (WPGMA, with ‘weighted’ as the parameter in clustergram function at Matlab 2019b) was applied together with the linkage method. In the Cristiano et al. dataset, one-way ANOVA ($p\text{-value} \leq 0.01$) was applied to select the hotspots that showed the group-specific fragmentation patterns. Further, hotspots are ranked by the z-score difference between the samples within the group and outside the group. The top 5,000 hotspots in each group were finally visualized in the figure.

The t-SNE Visualization of the cfDNA Fragmentation Hotspots Across Different Diseases.

[0145] T-SNE (tsne function at Matlab 2019b) was utilized for the dimensionality reduction and visualization of the fragmentation dynamics in the hotspots across multiple cancer and healthy conditions. Hotspots with a $p\text{-value} \leq 0.01$ (one-way ANOVA) were used for the analysis. Distance

similarity was calculated by the Spearman correlation together with default parameters (tsne function at Matlab 2019b).

The Gene Ontology Analysis of the cfDNA Fragmentation Hotspots.

[0146] Gene Ontology (GO) analysis of the cfDNA fragmentation hotspots was performed by GREAT (v4.04) [51]. The GO Biological Processes (GO BP) with a q-value of less than 0.01 (binomial test) were selected. Only the top ten GO BPs were shown in the main figure.

The Motif Analysis of the cfDNA Fragmentation Hotspots.

[0147] Motif analysis of cfDNA fragmentation hotspots was performed by HOMER (v4.11) with the command ‘findMotifsGenome.pl hotspots_file hg19 output_file-size given’[52]. Only motifs with a q-value of less than 0.01 were kept. Only the top 10 enriched motifs were shown in the figures.

The Estimation of Tumor Fractions by ichorCNA.

[0148] The ichorCNA v0.2.0[33] was run at 1 Mb resolution with the normalization by the normal panel provided in the package together with G+C %, mappability, and the following parameters: --normal “c (0.75)” --ploidy “c(2)” --maxCN 5 --estimateScPrevalence FALSE --scStates “c(1, 3)” --chrs “c(1:22)”

Application to Non-Malignant Diseases

[0149] In non-malignant diseases such as multiple sclerosis (MS), the changes in IFS in cfDNA fragmentation hotspots showed distinct patterns across MS disease subtypes indicating the potentially generalizable application to fine-scale fragmentation patterns to monitor the progression of complex diseases.

Example Computing Environments

[0150] The current disclosure provides methods and systems for identifying DNA fragmentation hotspots as part of diagnosing early stage cancer. The computing engines, modules, machine learning modules, machine learning engines, deep learning modules/engines, training systems, architectures and other disclosed functions are embodied as computer instructions that may be installed for running on one or more computer devices and/or computer servers. In some instances, a local user can connect directly to the system; in other instances, a remote user can connect to the system via a network.

[0151] Example networks can include one or more types of communication networks. For example communication networks can include (without limitation), the Internet, a local area network (LAN), a wide area network (WAN), various types of telephone networks, and other suitable mobile or cellular network technologies, or any combination thereof. Communication within the network can be realized through any suitable connection (including wired or wireless) and communication technology or standard (wireless fidelity (WiFi®), 4G, 5G, long-term evolution (LTE™)), and the like as the standards develop.

[0152] The computer device(s) and/or computer server(s) can be configured with one or more computer processors and a computer memory (including transitory computer memory and/or non-transitory computer memory), configured to perform various data processing operations. The computer device(s) and/or computer server(s) also include a network

communication interface to connect to the network(s) and other suitable electronic components.

[0153] Example local and/or remote user devices can include a personal computer, portable computer, smartphone, tablet, notepad, dedicated server computer devices, any type of communication device, and/or other suitable compute devices.

[0154] The computer device(s) and/or computer server(s) can include one or more computer processors and computer memories (including transitory computer memory and/or non-transitory computer memory), which are configured to perform various data processing and communication operations associated with diagnosing liver disease as disclosed herein based upon information obtained/provided over the network, from a user and/or from a storage device. In some implementations, storage device can be physically integrated to the computer device(s) and/or computer server(s); in other implementations, storage device can be a repository such as a Network-Attached Storage (NAS) device, an array of hard-disks, a storage server or other suitable repository separate from the computer device(s) and/or computer server(s).

[0155] In some instances, storage device can include the machine-learning models/engines and other software engines or modules as described herein. Storage device can also include sets of computer executable instructions to perform some or all the operations described herein.

[0156] The following list of reference has been cited herein by their number. Each reference below is incorporated herein by reference:

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What is claimed is:

1. A method for identifying DNA fragmentation hotspots as part of diagnosing early stage cancer, comprising:
de-novo characterizing genome-wide cell-free DNA fragmentation hotspots from whole-genome sequencing by integrating fragment size and coverage into a score; and identifying DNA fragmentation hotspots of interest based upon the score being below a threshold.
2. The method of claim 1, wherein the score identifies regions with lower fragment coverage and smaller fragment size.
3. The method of claim 1, further comprising a step of scanning a chromosome with a sliding window of a first size and a step with a second size.
4. The method of claim 3, wherein the score is calculated by weighting fragment coverage based on a ratio of average fragment size in the sliding window versus that in the whole chromosome
5. The method of claim 4, wherein the score is calculated based upon the following equation wherein, in the i_{th} window:

$$IFS_i = n_i * \left(1 + \frac{l_i}{L}\right) \quad (1)$$

$$C_i = \lfloor IFS_i \rfloor \quad (2)$$

wherein C_i is the IFS score round down to the nearest integer in the i_{th} window, n_i is the number of fragments whose mid-points are located within the i_{th} window, l_i is the average fragment size in the i_{th} window, L is the average fragment size in the whole chromosome.

6. The method of claim 4, further comprising utilize identified DNA fragmentation hotspots for the detection and localization of multiple early-stage cancers.
7. The method of claim 3, wherein the first size is 200 bp and the second size is 20 bp.
8. The method of claim 1, further comprising utilize identified DNA fragmentation hotspots for the detection of early-stage cancer.

9. The method of claim 8, wherein the detection step includes one or more steps taken from the group comprising: performing Gene Ontology (GO) analysis of the identified

DNA fragmentation hotspots; or
performing Motif analysis of the identified DNA fragmentation hotspots.

10. The method of claim 1, wherein integrating step weighs fragment coverages with size information.

11. The method of claim 10, wherein the integrating step weighs the fragment coverage based on a ratio of fragment size in a window versus that in the whole chromosome.

12. The method of claim 1, further comprising filtering out dark regions and low mappability regions.

13. A method for identifying genomic regions with higher fragmentation rates than the local and global backgrounds as part of diagnosing early stage cancer, comprising:

de-novo characterizing genome-wide cell-free DNA fragmentation regions with higher fragmentation rates than the local and global backgrounds from whole-genome sequencing by weighing the fragment coverages in each region by a ratio of average fragment sizes in the region versus that in the whole chromosome to generate a score; and

identifying DNA fragmentation regions of interest based upon comparing the score with a threshold.

14. The method of claim 13, further comprising a step of scanning a chromosome with a sliding window of a first size and a step with a second size.

15. The method of claim 14, wherein the score is calculated by weighting fragment coverage based on a ratio of average fragment size in the sliding window versus that in the whole chromosome

16. The method of claim 14, wherein the first size is 200 bp and the second size is 20 bp.

17. The method of claim 13, further comprising utilize identified DNA fragmentation hotspots for the detection of early-stage cancer.

18. The method of claim 17, wherein the detection step includes one or more steps taken from the group comprising: performing Gene Ontology (GO) analysis of the identified

DNA fragmentation hotspots; or
performing Motif analysis of the identified DNA fragmentation hotspots.

19. The method of claim 13, further comprising filtering out dark regions and low mappability regions.

20. A non-transitory computer memory including computer instructions for performing a method for identifying genomic regions with higher fragmentation rates than the local and global backgrounds as part of diagnosing early stage cancer, the computer instructions configured to perform steps of:

de-novo characterizing genome-wide cell-free DNA fragmentation regions with higher fragmentation rates than the local and global backgrounds from whole-genome sequencing by weighing the fragment coverages in each region by a ratio of average fragment sizes in the region versus that in the whole chromosome to generate a score; and

identifying DNA fragmentation regions of interest based upon comparing the score with a threshold.

21. The non-transitory computer memory of claim 20, wherein the computer instructions are further configured to perform a step of scanning a chromosome with a sliding window of a first size and a step with a second size.

22. The non-transitory computer memory of claim **21**, wherein the score is calculated by weighting fragment coverage based on a ratio of average fragment size in the sliding window versus that in the whole chromosome

23. The non-transitory computer memory of claim **21**, wherein the first size is 200 bp and the second size is 20 bp.

24. The non-transitory computer memory of claim **20**, wherein the computer instructions are further configured to utilize identified DNA fragmentation hotspots for the detection of early-stage cancer.

25. The non-transitory computer memory of claim **24**, wherein the detection step includes one or more steps taken from the group comprising:

performing Gene Ontology (GO) analysis of the identified

DNA fragmentation hotspots; or

performing Motif analysis of the identified DNA fragmentation hotspots.

26. The non-transitory computer memory of claim **20**, wherein the computer instructions are further configured to filter out dark regions and low mappability regions.

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