

ARRAYS TARGETING DIFFERENTIALLY ACCESSIBLE CHROMATIN REGIONS USING QUANTITATIVE POLYMERASE CHAIN REACTION

1. CROSS-REFERENCE OF RELATED APPLICATIONS

[0001] This application claims the benefit of and priority to U.S. Provisional Application No.: 63/494,387, filed April 5, 2023, which is hereby incorporated by reference in its entirety.

2. SEQUENCE LISTING

[0002] This instant application contains a Sequence Listing which has been submitted via Patent Center and is hereby incorporated by reference in its entirety. Said XML copy, created on April 2, 2024, is named 55154WO_CRF_sequencelisting, and is 27,347 bytes in size.

3. TECHNICAL FIELD

[0003] The present disclosure relates to arrays targeting differentially accessible chromatin regions using, for example, quantitative polymerase chain reaction (qPCR), when the number of differentially represented regions are, for example, fewer than 100. The disclosure also relates to methods of using such arrays to, for example, guide chemotherapy or immunotherapy in cancer (*e.g.*, gastrointestinal cancer and/or pancreatic ductal adenocarcinoma).

4. BACKGROUND

[0004] Pancreatic ductal adenocarcinoma (PDAC) is a lethal malignancy of the pancreas, with 66,440 new cases reported last year in the United States alone. By 2030, this disease is projected to surpass breast, prostate and colorectal cancer to become the second leading cause of cancer-related death in the United States. Almost 80% of patients are clinically presented as surgically non-resectable metastatic diseases. In the remaining resectable subset, the disease recurs in approximately 50% of cases within the first year of surgery despite adjuvant chemotherapy, another 30-40% recurs within next 2-5 years, whereas a small subset (10-15%) shows long-term disease-free survival (DFS) of more than 10 years.

[0005] Identification of patients at risk for recurrence, and particularly early recurrence in PDAC, and also in other types of cancers, in a timely manner is critical for reducing healthcare costs. Therefore, there is a need for approaches to identify such patients and tailor treatment accordingly.

5. SUMMARY

[0006] In one aspect, described herein are methods for determining a prognostic score indicative of a subject's responsiveness to one or more treatment modalities or indicative of a duration of disease-free survival, the method comprising:

(a) contacting a biological sample obtained from the subject with a transposase complex to produce a population of tagged DNA fragments representing accessible chromatin regions of the intact nuclei or intact nucleosome structure, wherein the biological sample comprises pancreatic ductal adenocarcinoma cells having morphologically intact nuclei or intact nucleosomes,

(b) hybridizing a set of targeting oligonucleotide probes to a specific region on the accessible chromatin regions to generate targeted accessible chromatin region fragments, wherein the targeting oligonucleotide probes specifically target differentially accessible chromatin regions, wherein the targeting oligonucleotide probes comprise:

(i) a first subset of oligonucleotide probes targeting accessible chromatin regions associated with a first phenotype, and

(ii) a second subset of oligonucleotide probes targeting accessible chromatin regions associated with a second phenotype;

(c) amplifying the targeted accessible chromatin region fragments obtained in (b) that are associated with the first phenotype and the second phenotype; and

(d) determining a prognostic score based on epigenetic signature values of the biological sample,

wherein the prognostic score is determined based on a differential of a first epigenetic signature value and a second epigenetic signature value,

wherein the prognostic score is indicative of the subject's responsiveness to the one or more treatment modalities or indicative of a duration of disease-free survival.

[0007] In one aspect, described are methods of treating a subject having, or suspected of having, pancreatic ductal adenocarcinoma with one or more treatment modalities, the method comprising:

(a) receiving a prognostic score indicative of the subject's responsiveness to one or more treatment modalities or indicative of a duration of disease-free survival,

wherein the prognostic score is determined based on epigenetic signature values of a biological sample from the subject that comprises pancreatic ductal adenocarcinoma cells

having morphologically intact nuclei or intact nucleosomes, the biological sample having been contacted with a transposase complex to produce a population of tagged DNA fragments representing accessible chromatin regions of the intact nuclei or intact nucleosome structure,

wherein a set of targeting oligonucleotide probes were hybridized to a specific region on the accessible chromatin regions to generate targeted accessible chromatin region fragments,

wherein the targeting oligonucleotide probes specifically target differentially accessible chromatin regions,

wherein the prognostic score is determined based on a differential of a first epigenetic signature value and a second epigenetic signature value; and

(b) treating the subject with the one or more treatment modalities based on the prognostic score.

[0008] In accordance with any one of the embodiments, the method further comprising, prior to step (a), enriching the biological sample for tumor cells.

[0009] In accordance with any one of the embodiments, the method further comprising contacting the biological sample with an agent to isolate tumor cells from non-tumor cells in the biological sample to enrich the sample for tumor cells.

[0010] In some embodiments, the agent comprises antibody-conjugated magnetic beads, EpCAM-conjugated magnetic beads, or a combination thereof.

[0011] In accordance with any one of the embodiments, the method further comprising:

- (i) attaching a detectable label to the tagged DNA fragments to produce labeled fragments; and
- (ii) contacting the detectable labeled fragments to the set of targeting oligonucleotide probes.

[0012] In accordance with any one of the embodiments, the method further comprising quantifying the amount of amplified targeted accessible chromatin region fragments to obtain the first epigenetic signature value and the second epigenetic value.

[0013] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes are selected from any pair of oligonucleotide probes in Table 4.

[0014] In accordance with any one of the embodiments, the targeting oligonucleotide probes comprises a nucleic acid sequence having a sequence of any one of SEQ ID NOs.: 1-30.

[0015] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of ARHGEF10, CLDN23, C12orf36, and SPATA4.

[0016] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, and ITGAV.

[0017] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of GTF3C6, LINC01703, C1orf131, and XRCC2.

[0018] In accordance with any one of the embodiments, the accessible chromatin regions are selected from any one of the accessible chromatin regions in FIG. 9A, FIG. 9B, and/or Table 3.

[0019] In some embodiments, the accessible chromatin regions are selected from any one of the accessible chromatin regions in Table 3.

[0020] In accordance with any one of the embodiments, the method further comprising the step of comparing the first epigenetic signature value to the second epigenetic signature value to obtain a differential value.

[0021] In accordance with any one of the embodiments, the method further comprising normalizing the differential value with at least one of a positive control value and one of a negative control value to obtain the prognostic score.

[0022] In some embodiments, the prognostic score is at least 0.6.

[0023] In some embodiments, the method further comprising detecting nuclear localization of at least one of a transcription factor selected from any one of the transcription factors in Tables 2A and 2B.

[0024] In some embodiments, the transcription factors are selected from ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6,

GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFX3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.

[0025] In some embodiments, the transcription factors are selected from ZKSCAN1A, HNF1B, or a combination thereof.

[0026] In accordance with any one of the embodiments, the method further comprising predicting a long duration of disease-free survival when the first epigenetic signature value is significantly higher than the second epigenetic signature value and/or predicting a short duration of disease-free survival when the second epigenetic signature value is significantly higher than the first epigenetic value.

[0027] In accordance with any one of the embodiments, the first phenotype is recurrence of a cancer within one year of surgical resection and the second phenotype is non-recurrence of a cancer within one year of surgical resection.

[0028] In accordance with any one of the embodiments, the first phenotype is non-responder and the second phenotype is responder to a cancer therapy.

[0029] In some embodiments, the cancer therapy is selected from chemotherapy, immunotherapy, radiation, or combinations thereof.

[0030] In accordance with any one of the embodiments, the second phenotype is having a median disease-free survival of between 50 to 1500 days.

[0031] In accordance with any one of the embodiments, the second phenotype is having a median disease-free survival of at least 350 days.

[0032] In accordance with any one of the embodiments, the first phenotype is having a median disease-free survival of between 1 to 350 days.

[0033] In accordance with any one of the embodiments, the first phenotype is having a median disease-free survival of less than 50 days.

[0034] In accordance with any one of the embodiments, the biological sample comprises treatment-naïve malignant cells.

[0035] In accordance with any one of the embodiments, the subject is a treatment naïve patient who has not received the one or more treatment modalities.

[0036] In accordance with any one of the embodiments, the subject is under treatment or has been treated with the one or more treatment modalities.

[0037] In accordance with any one of the embodiments, the one or more treatment modalities are selected from resecting cancerous tissue, neo-adjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, an epigenetic drug, or combinations thereof.

[0038] In some embodiments, the epigenetic drug is selected from DNMT inhibitor, an HDAC inhibitor, an EZH2 inhibitor, or combinations thereof.

[0039] In some embodiments, the neo-adjuvant chemotherapy and/or adjuvant chemotherapy is selected from gemcitabine, nab-paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, leucovorin, capecitabine, cisplatin, or combinations thereof.

[0040] In accordance with any one of the embodiments, the biological sample is selected from a tumor biopsy or surgically resected tumor specimen.

[0041] In accordance with any one of the embodiments, the method does not include sequencing the tagged fragments or amplicons thereof. In accordance with any one of the embodiments, the amplified targeted accessible chromatin fragments comprise a mean size of about 120 bp.

[0042] In accordance with any one of the embodiments, obtaining the targeted accessible chromatin region fragments does not include the step of sequencing the tagged fragments or amplicons thereof.

[0043] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.

[0044] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is about 12.

[0045] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis or poor prognosis is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.

[0046] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis is about 3.

[0047] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining poor prognosis is about 8.

[0048] In one aspect, described are kits for determining an epigenetic landscape associated with a specific phenotypic trait of a biological sample, the kit comprising:

- (a) an array configured to detect targeted accessible chromatin region fragments obtained from the biological sample, wherein the array comprises a panel of sets of targeting oligonucleotide probes specifically targeting differentially accessible chromatin regions;
- (b) reagents; and
- (c) instructions for amplifying and quantifying the targeted accessible chromatin region fragments to obtain a first epigenetic signature value and a second epigenetic value.

[0049] In some embodiments, the panel of targeting oligonucleotide probes is arranged as described in FIG. 4A or 4B.

[0050] In one aspect, described are kits for determining an epigenetic landscape associated with a specific phenotypic trait of a biological sample, the kit comprising:

- (a) one or more sets of targeting oligonucleotide probes for detect targeted accessible chromatin region fragments obtained from the biological sample, wherein the targeting oligonucleotide probes specifically target and amplify differentially accessible chromatin regions to generate one or more targeted accessible chromatin region fragments;
- (b) reagents; and
- (c) instructions for amplifying and quantifying the targeted accessible chromatin region fragments to obtain a first epigenetic signature value and a second epigenetic value.

[0051] In accordance with any one of the embodiments, the biological sample comprises pancreatic ductal adenocarcinoma cells having morphologically intact nuclei or intact nucleosome (histone-DNA) structure.

[0052] In accordance with any one of the embodiments, the kit further comprising reagents and instruction for obtaining the biological sample by contacting the morphologically intact nuclei or intact nucleosome (histone-DNA) structure to a transposase complex to produce a population of tagged DNA fragments representing the targeted accessible chromatin region fragments.

[0053] In accordance with any one of the embodiments, the targeting oligonucleotide probes comprises a nucleic acid sequence having a sequence of any one of SEQ ID NOs.: 1-30.

[0054] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of ARHGEF10, CLDN23, C12orf36, and SPATA4.

[0055] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, and ITGAV.

[0056] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of GTF3C6, LINC01703, C1orf131, and XRCC2.

[0057] In accordance with any one of the embodiments, further comprising reagents and instructions for enriching the biological sample obtained from the subject for tumor cells.

[0058] In some embodiments, the reagents comprise antibody-conjugated magnetic beads, EpCAM-conjugated magnetic beads, or a combination thereof to isolate tumor cells from non-tumor cells in the biological sample.

[0059] In accordance with any one of the embodiments, the kit further comprising reagents and instructions for:

- (i) attaching a detectable label to the tagged DNA fragments to produce labeled fragments; and
- (ii) contacting the detectable labeled fragments to the set of oligonucleotide probes.

[0060] In accordance with any one of the embodiments, the kit further comprising instructions for determining a prognostic score indicative of the subject's responsiveness to one or more treatment modalities based on a differential score of the first epigenetic signature value and the second epigenetic value.

[0061] In accordance with any one of the embodiments, the instruction comprises normalizing the differential value with at least one of a positive control value and a negative control value to obtain the prognostic score.

[0062] In some embodiments, the prognostic score is at least 0.6.

[0063] In accordance with any one of the embodiments, the kit further comprising reagents and instructions for detecting nuclear localization of a transcription factor selected from any one of transcription factors in Tables 2A and 2B.

[0064] In some embodiments, the transcription factors are selected from ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5,

AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFHX3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.

[0065] In some embodiments, the transcription factors are selected ZKSCAN1A, HNF1B, or a combination thereof.

[0066] In accordance with any one of the embodiments, the kit further comprising reagents and instructions for predicting a long duration of disease-free survival when the first epigenetic signature value is significantly higher than the second epigenetic signature value and/or predicting a short duration of disease-free survival when the second epigenetic signature value is significantly higher than the first epigenetic value.

[0067] In accordance with any one of the embodiments, the kit further comprising reagents and instructions for determining a first phenotype and second phenotype of the subject's responsiveness to one or more treatment modalities.

[0068] In some embodiments, the first phenotype is recurrence of a cancer within one year of surgical resection and the second phenotype is non-recurrence of a cancer within one year of surgical resection.

[0069] In some embodiments, the first phenotype is non-responder and the second phenotype is responder to a cancer therapy.

[0070] In some embodiments, the cancer therapy is selected from chemotherapy, immunotherapy, radiation, or combinations thereof.

[0071] In accordance with any one of the embodiments, the second phenotype is having a median disease-free survival of between 50 to 1500 days.

[0072] In accordance with any one of the embodiments, the second phenotype is having a median disease-free survival of at least 350 days.

[0073] In accordance with any one of the embodiments, the first phenotype is having a median disease-free survival of between 1 to 350 days.

[0074] In accordance with any one of the embodiments, the first phenotype is having a median disease-free survival of less than 50 days.

[0075] In accordance with any one of the embodiments, the biological sample comprises treatment-naïve malignant cells.

[0076] In some embodiments, the subject is a treatment naïve patient who has not received the one or more treatment modalities.

[0077] In accordance with any one of the embodiments, the subject is under treatment or has been treated with the one or more treatment modalities.

[0078] In accordance with any one of the embodiments, the one or more treatment modalities are selected from resecting cancerous tissue, neo-adjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, an epigenetic drug, or combinations thereof.

[0079] In some embodiments, the epigenetic drug is selected from DNMT inhibitor, an HDAC inhibitor, an EZH2 inhibitor, or combinations thereof.

[0080] In some embodiments, the neo-adjuvant chemotherapy and/or adjuvant chemotherapy is selected from gemcitabine, nab-paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, leucovorin, capecitabine, cisplatin, or combinations thereof.

[0081] In accordance with any one of the embodiments, the biological sample is selected from a tumor biopsy or surgically resected tumor specimen.

[0082] In accordance with any one of the embodiments, obtaining the targeted accessible chromatin region fragments does not include sequencing the tagged fragments or amplicons thereof.

[0083] In accordance with any one of the embodiments, the amplified targeted accessible chromatin fragments comprise a mean size of about 120 bp.

[0084] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.

[0085] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is about 12.

[0086] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis or poor prognosis is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.

[0087] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis is about 3.

[0088] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining poor prognosis is about 8.

[0089] In one aspect, this disclosure provides a low-cost array targeting fewer than 100 differentially accessible chromatin regions by qPCR. The differentially accessible chromatin regions may be identified using Assay for Transposase-Accessible Chromatin-sequencing (ATAC-seq) or Assay for Transposase-Accessible Chromatin-array (ATAC-array); the array may be a “targeted ATAC-qPCRarray.” Such arrays, unlike ATAC-seq or ATAC-array, detect only the “targeted” accessible chromatin regions of interest, particularly valuable when the differentially accessible regions are fewer than 100. ATAC-array, a hybridization-based reading of chromatin accessibility suitable for reading the chromatin signature more than 100 regions is described in WO2020036929A1, or US20210324376A1, or Dhara *et al.* Pancreatic cancer prognosis is predicted by an ATAC-array technology for assessing chromatin accessibility. *Nat Commun* 12, 3044 (2021), or by ATAC-seq as described in Shin *et al.* Chromatin accessibility of circulating CD8⁺ T cells predicts treatment response to PD-1 blockade in patients with gastric cancer. *Nat Commun* 12, 975 (2021), each of which is incorporated herein by reference in its entirety.

[0090] In one aspect, this disclosure provides methods for guiding cancer treatment (e.g., guiding chemotherapy and/or immunotherapy). In certain embodiments, an array disclosed herein is used to guide cancer treatment. For example, an array can be a prognostic tool in the field of precision oncology, associating a specific set of open chromatin regions of the functional genome with specific disease phenotypes or response to a specific regimen of drug, or combination of drugs. Although gene expression signatures associated with prognosis have been described in malignant diseases, unlike gene expression signature, which is an RNA-based technology, chromatin accessibility signature is a DNA-based technology therefore more robust and better applicability in routine clinical specimens.

[0091] In one aspect, described herein are methods for determining an epigenetic landscape associated with a specific phenotypic trait of a biological sample, the method comprising: (a) providing a biological sample comprising morphologically intact nuclei or intact nucleosome (histone-DNA) structure; (b) contacting the intact nuclei or intact nucleosome to a transposase complex to produce a population of tagged DNA fragments representing accessible chromatin regions (ACRs) of the intact nuclei and/or intact nucleosome (histone-DNA) structure; (c) hybridizing a set of targeting

oligonucleotide probes to a specific region on the ACRs to generate targeted ACR fragments, wherein the targeting oligonucleotide probes specifically targets no more than 100 differentially accessible chromatin regions selected from Table 1 or Table 2, wherein the targeting oligonucleotide probes comprise: (i) a first subset of oligonucleotide probes targeting ACRs associated with a first phenotype, and (ii) a second subset of oligonucleotide probes targeting ACRs associated with a second phenotype; (d) amplifying the targeted ACR fragments associated with the first phenotype and the second phenotype obtained in (c); and (e) quantifying the amount of amplified targeted ACR fragments, thereby determining the epigenetic landscape associated with the first and the second phenotypic traits of the biological sample. In some embodiments, the amplification fragment comprises a mean size of less than 100 bp.

[0092] In accordance with any of the embodiments, the first phenotype is recurrence of a cancer within one year of surgical resection and the second phenotype is non-recurrence of a cancer within one year of surgical resection.

[0093] In accordance with any of the embodiments, the first phenotype is non-responder, and the second phenotype is responder to a cancer therapy. In some embodiments, the cancer therapy is selected from chemotherapy, immunotherapy, and radiation.

[0094] In accordance with any of the embodiments, the method further comprises assessing nuclear localization of one or more biomarkers capable of modulating gene expression through complementary binding to one or more specific regions on the amplified targeted ACR fragments. In some embodiments, the biomarker is a transcription factor. In some embodiments, the transcription factor is selected from ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFH3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.

[0095] In accordance with any of the embodiments, the biological sample is selected from a tumor biopsy, surgically resected tumor specimen, liquid biopsy, bodily fluid, blood, plasma, saliva, semen, vaginal discharge, urine, circulating shedding tumor tissue, and/or circulating tumor DNA (ctDNA).

[0096] In accordance with any of the embodiments, the biological sample is pancreatic ductal adenocarcinoma tissue.

[0097] In accordance with any of the embodiments, the biological sample comprises treatment-naïve malignant cells.

[0098] In accordance with any of the embodiments, the biological sample is collected from a patient who had been treated with one or more treatment modalities.

[0099] In accordance with any of the embodiments, the phenotypic trait is responsiveness to a treatment modality. In some embodiments, the treatment modality is selected from the group consisting of surgical resection, chemotherapy, radiation, immunotherapy, and a combination thereof.

[00100] In accordance with any of the embodiments, the method further comprises isolating nucleosomal DNA from the cell nuclei of the biological sample. In some embodiments, the nuclei are isolated in a manner that maintains nucleosome structure.

[00101] In accordance with any of the embodiments, the method does not include sequencing the tagged fragments or amplicons thereof.

[00102] An epigenetic landscape integrates the entire ensemble of epigenetic silencing and/or activating events in the genome (e.g., through methylation and acetylation together). In certain embodiments, the epigenetic landscape is assessed by a qPCR-based platform described herein, generally referred to as “ATAC-qPCRarray.” One exemplary application of the ATAC-qPCRarray technology is as a diagnostic test that can be performed on tumor biopsies or surgically resected tumor specimens, or liquid biopsies. Typically, results are provided within a day.

[00103] In an exemplary embodiment, an epigenetic landscape is significantly associated with prognosis and, in particular, early disease recurrence (*i.e.*, within 1 year of surgery) in PDAC patients even after apparently complete surgical removal (R0 margin-negative resection) of the primary tumor, and in spite of adjuvant chemotherapy (*e.g.*, gemcitabine). The epigenetic landscape may comprise at least 700 functionally relevant regulatory regions silenced and at least 300 other functionally relevant regulatory regions accessible in patients who did not respond to their first-line of chemotherapy (gemcitabine). Another exemplary embodiment, an epigenetic landscape is predictive of immunotherapy (immune checkpoint inhibition (ICI) therapy). The epigenetic landscape may comprise at 67 functionally relevant regulatory regions predicts with high sensitivity (100.0%) and specificity (90.9%) for distinguishing responder from non-responder to ICI drug pembrolizumab.

6. BRIEF DESCRIPTION OF THE DRAWINGS

[00104] For a better understanding of the invention, reference may be made to embodiments shown in the following drawings. The components in the drawings are not necessarily to scale and related elements may be omitted, or in some instances proportions may have been exaggerated, so as to emphasize and clearly illustrate the novel features described herein. In addition, system components can be variously arranged, as known in the art.

[00105] FIGs. 1A-1B illustrate representation of the 1092 differentially accessible chromatin peaks identified by ATAC-seq in pancreatic cancer patients (FIG. 1B) from the near-saturation identification of 121697 open chromatin peaks across the genome (FIG. 1A).

[00106] FIGs. 2A-2B depict a schematic representation of an ATAC-array (FIG. 2A) and the correlation of the ATAC-seq (FIG. 2B) confined to the signature regions.

[00107] FIGs. 3A-3B depict histogram results of the ATAC-array showing the differential enrichment of peaks from a poor-prognosis (FIG. 3A) and better-prognosis (FIG. 3B) pancreatic cancer patient.

[00108] FIGs. 4A-4B depict a schematic representation of an exemplary ATAC-qPCR array approach described herein, where (FIG. 4A) 96-well format and (FIG. 4B) is 384-well format.

[00109] FIG. 5 depicts sixty (60) TFs identified whose motifs were differentially open in recurrent (17 motifs) and non-recurrent (44 motifs) patients.

[00110] FIG. 6 provides a K-M graph showing significant segregation of good prognosis and poor prognosis. P value = 0.0019.

[00111] FIGs. 7A and 7B provide results of melting curve analysis showing a single peak for each primer set.

[00112] FIG. 8 shows K-M graph showing the long-term ($n=7$) and short-term ($n=7$) survivor patients selected for the validation of the targets. P value = 0.00014.

[00113] FIGs. 9A and 9B show results from ATAC-qPCR analysis of the 11 target regions normalized with the 4 control regions.

[00114] FIG. 10 shows Box plot showing the significant difference (t test $p=0.034$) in PS between good and poor prognosis patients. P value = 0.034.

7. DETAILED DESCRIPTION

[00115] This detailed description is intended only to acquaint others skilled in the art with the present invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This description and its examples are intended for purposes of illustration only. This invention, therefore, is not limited to the embodiments described in this patent application, and may be variously modified.

7.1 Definitions

[00116] As used in the specification and the appended claims, unless specified to the contrary, the following terms have the meaning indicated:

[00117] The term “about” as used herein, means approximately, and in most cases within 10% of the stated value.

[00118] The term “qPCRarray” is intended to describe a two-dimensional or three-dimensional arrangement of addressable regions bearing oligonucleotides associated with that region. The accessible regions from an ATAC library prepared from specimens will be amplified by quantitative polymerase chain reaction with a set of specifically designed oligonucleotide primers complementary to the accessible regions (signatures with high predictive ability of prognosis and/or drug response)

[00119] The term “biological sample” is to be understood as any *in vivo*, *in vitro*, or *in situ* sample of one or more cells or cell fragments. This can, for example, be a unicellular or multicellular organism, blood sample, biopsied tissue sample, tissue section, cytological sample, or any derivative of the foregoing (*e.g.*, a subsample, portion, or purified cell population). In certain embodiments, a biological sample is obtained from a mammal, including, but not limited to, a primate (including human), mouse, rat, cat, or dog.

[00120] The term “cancer” includes, but is not limited to, breast cancer, colorectal cancer, esophageal cancer, gallbladder cancer, gastric cancer, leukemia (*e.g.*, acute myeloid leukemia (AML) or chronic myeloid leukemia (CML)), liver cancer (*e.g.*, hepatocellular carcinoma (HCC)), lung cancer (*e.g.*, non-small cell lung cancer (NSCLC) or small cell lung cancer (SCLC)), lymphoma (*e.g.*, non-Hodgkin lymphoma), ovarian cancer, pancreatic cancer, and prostate cancer. The term “cancer” also includes cancer metastasis of a primary tumor such as primary pancreatic cancer. Thus, if

reference is made, for example, to pancreatic cancer, this also includes metastasis of the pancreatic cancer, for example metastasis to the lung, liver and/or lymph nodes.

[00121] The term “detectable label” refers to a moiety that can be attached directly or indirectly to an oligomer, such as an oligonucleotide, to thereby render the oligomer detectable by an instrument or method.

[00122] The term “transposase complex” refers to a complex that contains a transposase (which typically exists as a dimer of transposase polypeptides) that is bound to at least one adapter. The term “adapter” refers to a nucleic acid molecule that is capable of being attached to a polynucleotide of interest. An adapter can be single stranded or double stranded, and it can comprise DNA, RNA, and/or artificial nucleotides. The adapter can add one or more functionalities or properties to the polynucleotide of interest, such as providing a priming site for amplification or adding a barcode. By way of example, adapters can include a universal priming site for amplification. By way of further example, adapters can include one or more barcode of various types or for various purposes, such as molecular barcodes, sample barcodes and/or target-specific barcodes. In practice, a transposase complex can be used to attach an adapter to the end of a DNA fragment generated by the enzymatic action of the transposase.

[00123] The terms “treat”, “treating” and “treatment” refer to a method of alleviating or abrogating a condition, disorder, or disease and/or the attendant symptoms thereof.

[00124] The term “accessible chromatin regions” or “ACR” or “open chromatin regions” refer to regions of DNA within a cell’s nucleus that are loosely packaged and available to proteins involved in transcription.

[00125] The terms “chromatin accessibility patterns” refers to “open chromatin” or “close chromatin” patterns.

[00126] The term “open chromatin” or “euchromatin” refers to regions of DNA within the nucleus that are loosely packaged and readily accessible to transcription. The regions are typically associated with genes that are expressed or active within a cell.

[00127] The term “close chromatin” or “heterochromatin” refers to regions of DNA within the cell’s nucleus being tightly packaged, which hinders the access of proteins for transcription. The regions are typically associated with genes that are repressed or inactive within a cell.

[00128] The term “chromatin accessibility signature” refers to a defined set of accessible chromatin regions (ACRs) that are differentially represented, showing a defined pattern (signature) statistically associated (or correlated) with a specific phenotype. For example, as published in Dhara et al., Nature Communications 2021, 1092 differentially represented ACRs are correlated with pancreatic cancer patients who responded or non-responded to chemotherapy.

[00129] The term “epigenetic signature value” refers to a median value of a set of accessible chromatin regions indicating a good prognosis (e.g., set of blue regions) or a median value of a set of accessible chromatin regions indicating a poor prognosis (e.g., set of red regions). For example, the median prognosis value of a set of accessible chromatin regions indicating a good prognosis is the median value of at least 3 replications of ATAC-qPCR array (e.g., the median Ct value) of the accessible chromatin regions selected from at least one of CLDN23, SPATA4, ARHGEF-10, and C12orf36. Conversely, the median prognosis value of a set of accessible chromatin regions indicating a poor prognosis is the median value of at least 3 replications of ATAC-qPCR array analyses (e.g., the median Ct value) of the accessible chromatin regions selected from at least one of RN7SL, CNBP, MAP2K2, ITGAV, PPAP2B, FIG4, PAPL, and TTC19. A control epigenetic signature value refers to the median control value, which is the median prognosis value of a set of accessible chromatin regions indicating the median value of at least 3 replications of ATAC-qPCR array analyses (e.g., the median Ct value) of the accessible chromatin regions selected from at least one of GTF3C6, LINC01703, C1orf131, and XRCC2.

[00130] As used herein, the term “Ct value” refers to a cycle threshold or the number of cycles needed in a polymerase chain reaction (PCR) test to amplify a specific target molecule to a detectable level. In some embodiments, the Ct value indicates the amount of starting materials present in the sample. In the context of detecting accessible chromatin regions, the Ct value can reflect, for example, the availability of the chromatin region for transcription factor binding. A lower Ct value indicates fewer PCR cycles needed and can indicate a higher availability of accessible chromatin regions. A higher Ct value indicates more PCR cycles needed and can indicate a lower availability of accessible chromatin regions. In a qPCR analysis, a low 2^{-dCt} reflects fewer PCR cycles are needed to detect the target molecule (e.g., accessible chromatin region) in the sample and can indicate a higher initial amount or availability of the target molecule present in the sample. In the context of detecting accessible chromatin regions, a low 2^{-dCt} can represent a high relative abundance of the accessible chromatin region in the sample compared to the reference sample (e.g., control).

[00131] The term “prognostic score (PS)” refers to the difference between an epigenetic signature value of a good prognosis accessible chromatin region and an epigenetic signature value of a poor prognosis accessible chromatin region, and the difference is normalized with a control epigenetic signature value as illustrated in Section 7.2 and Example 5 herein. The prognostic score can be used to assess, determine, or predict a patient’s responsiveness to a treatment modality (e.g., chemotherapy, immunotherapy, or surgery). For example, a prognostic score of >0.6 indicates the patient has a good response to the treatment, while a prognostic of <0.6 indicates the patient has a poor prognosis to the treatment.

[00132] The term “differential value” refers to the difference between an epigenetic signature value of a good prognosis and an epigenetic signature value of poor prognosis. The differential value can be used to determine the prognostic scores with a range of values, for example, <0.6 non-responder indicates poor prognosis and >0.6 responder indicates good prognosis.

[00133] The term “responder” refers to a patient who has good responsiveness to a treatment modality described herein. A responder may have a DFS of at least 50 days, at least 400 days, or longer.

[00134] The term “non-responder” refers to a patient who has poor responsiveness to a treatment modality described herein. A non-responder may have a DFS of less than 400 days, less than 100 days, less than 50 days, or shorter.

[00135] In this application, the use of the disjunctive is intended to include the conjunctive. The use of definite or indefinite articles is not intended to indicate cardinality. In particular, a reference to “the” object or “a” and “an” object is intended to denote also one of a possible plurality of such objects. Further, the conjunction “or” may be used to convey features that are simultaneously present instead of mutually exclusive alternatives. In other words, the conjunction “or” should be understood to include “and/or.” The terms “includes,” “including,” and “include” are inclusive and have the same scope as “comprises,” “comprising,” and “comprise” respectively.

7.2 QPCR Array Methods

[00136] In one aspect, the present disclosure provides a method for analyzing chromatin accessibility. Chromatin may be present in the nuclei or in samples in which nucleosomal structure has been maintained (e.g., a product of lysed nuclei, or circulating tumor DNA (ctDNA)). In certain embodiments, the method comprises: (a) providing a biological sample comprising chromatin, such

as from morphologically intact nuclei; (b) fragmenting and tagging accessible chromatin regions (ACRs) to produce tagged fragments; (c) optionally, amplifying the tagged fragments; (d) hybridizing or attaching a set of oligonucleotide primers specifically designed to the ACRs; and (e) amplifying the ACRs by PCR master mix containing SYBR-green followed by detection of fluorescence intensities of SYBR-green by qPCR machine. In some embodiments, fragmenting and tagging ACRs comprising using enzymatic tagmentation such as using Tn transposase-based or restriction enzyme-based tagmentation. In some embodiments, fragmenting and tagging ACRs comprising using enzymatic tagmentation such as sonication, microfluidic shearing, or chemical cleavage (e.g., hydrogen peroxide, potassium permanganate). In certain embodiments, the method further comprises determining the accessibility of at least one chromatin region. In certain embodiments, the set of oligonucleotide probes represent chromatin regions that are differentially accessible between a first phenotype and a second phenotype (e.g., between treatment-resistant disease and treatment-sensitive disease; between a cancer likely to recur within one year following surgical resection and a cancer likely not to recur within one year following surgical resection). In some such embodiments, the set of oligonucleotide primers comprises (i) a first subset of oligonucleotide primers representative of accessible chromatin regions associated with the first phenotype and (ii) a second subset of oligonucleotide primers representative of accessible chromatin regions associated with the second phenotype.

[00137] In certain embodiments, the method does not include sequencing the tagged fragments or amplicons thereof.

[00138] In certain embodiments, at least some of the differentially accessible chromatin regions include a promoter, an enhancer, and/or other regulatory elements. In certain embodiments, the biological sample comprises malignant or diseased tissue. In other embodiments, the biological sample comprises normal tissue.

[00139] In certain embodiments, the method comprises providing a biological sample. The biological sample may be, for example, a blood sample, a tissue sample, or a cytological sample. In certain embodiments, the biological sample comprises cancerous cells or cells suspected of being cancerous. In some such embodiments, the biological sample is unprocessed. In other such embodiments, the biological sample is processed to, for example, isolate a specific cell population. For example, a population of Epithelial Cell Adhesion Molecule positive (EpCAM+) cells (i.e., cells expressing the transmembrane protein EpCAM) may be isolated from a tissue sample such as tissue biopsied from a pancreatic tumor or, more specifically, a pancreatic ductal adenocarcinoma, or CD8+

T-lymphocyte cells from peripheral blood of a patient. Without being bound to any theory, cancer cells may express more EpCAM compared to healthy cells. Isolating cells expressing EpCAM may enrich and isolate tumor cells from the biological sample.

[00140] In certain embodiments, the biological sample can be obtained from a patient diagnosed with cancer. For example, in case of pancreatic cancer a patient may be referred to undergo endoscopic ultrasound and fine needle aspiration (EUS-FNA) for tissue diagnosis of a suspected pancreatic mass, which may result in the diagnosis of PDAC. This EUS-FNA or the laparoscopic surgery tissue acquisition process occurs prior to chemotherapy treatment and may provide treatment-naïve malignant cells from all stages of PDAC.

[00141] In certain embodiments, the method further comprises isolating nucleosomal DNA from the biological sample, such as an isolated cell population, or peripheral blood. In some such embodiments, nuclei are isolated and/or lysed in a manner that maintains nucleosome structure.

[00142] Nuclei are isolated or collected in such a manner as to ensure that nucleosomal structure is maintained. Thus, nuclei comprise regions of tightly packed or closed chromatin and regions of loosely packed or open chromatin. In certain embodiments, the method comprises fragmenting open chromatin regions of nuclei to obtain a population of fragments representing the open chromatin regions. In certain embodiments, the method comprises tagging such fragments with, for example, an adapter. In certain embodiments, the fragmenting and tagging occurs substantially simultaneously or in rapid succession. Certain transposases such as a hyperactive Tn5 transposase, loaded *in vitro* with adapters, can substantially simultaneously fragment and tag DNA with the adapters. Thus, in some embodiments, the method may comprise “tagmenting” the open chromatin regions using, for example, a hyperactive Tn5 transposase loaded with one or more adapters.

[00143] In certain embodiments, the fragmenting and tagging step comprises contacting morphologically intact nuclei with a transposase complex. In some such embodiments, a transposase complex comprises a transposase enzyme (which is usually in the form of a dimer of transposase polypeptides) and a pair of adapters. In certain embodiments, isolated nuclei are lysed when contacted with a transposase complex and, thus, the method may comprise lysis of intact nuclei.

[00144] In certain embodiments, the transposase is prokaryotic, eukaryotic, or from a virus. In certain embodiments, the transposase is a hyperactive transposase. In certain embodiments, the transposase is an RNase transposase, such as a Tn transposase. In some such embodiments, the transposase is a Tn5 transposase or derived from a Tn5 transposase. In certain preferred embodiments,

the transposase is a hyperactive Tn5 transposase (*e.g.*, a Tn5 transposase having an L372P mutation). In certain embodiments, the transposase is a MuA transposase or derived from a MuA transposase. In certain embodiments, the transposase is a Vibhar transposase (*e.g.*, from *Vibrio harveyi*) or derived from a Vibhar transposase. In the above examples, a transposase derived from a parent transposase can comprise a peptide fragment with at least about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 91%, about 92%, about 93%, about 94%, about 95%, about 96%, about 97%, about 98%, or about 99% amino acid sequence homology and/or identity to a corresponding peptide fragment of the parent transposase. The peptide fragment can be at least about 10, about 15, about 20, about 25, about 30, about 35, about 40, about 45, about 50, about 60, about 70, about 80, about 90, about 100, about 150, about 200, about 250, about 300, about 400, or about 500 amino acids in length. For example, a transposase derived from Tn5 can comprise a peptide fragment that is 50 amino acids in length and about 80% homologous to a corresponding fragment in a parent Tn5 transposase.

[00145] In an exemplary method described herein, the transposase complex comprises a transposase loaded with two adapter molecules that each contain a recognition sequence at one end. The transposase catalyzes substantially simultaneous fragmenting of the sample and tagging of the fragments with sequences that are adjacent to the transposon recognition sequence (*i.e.*, “tagmentation”). In some cases, the transposase enzyme can insert the nucleic acid sequence into the polynucleotide in a substantially sequence-independent manner. In certain embodiments, a preliminary step includes loading a transposase with one or more oligonucleotide adapters. Typically, the adapters comprise oligonucleotides that have been annealed together so that at least the transposase recognition sequence is double stranded.

[00146] In certain embodiments, the amplifying step comprises an amplification reaction that results in a relatively uniform amplification of substantially all template sequences in a sample (*e.g.*, at least 85%, 90%, or 95% of the template sequences). In certain embodiments, the amplifying step comprises polymerase chain reaction (PCR). In certain embodiments, the amplifying step comprises PCR using primers specific for adapter sequences appended to the fragments during the fragmenting and tagging step.

[00147] Results from the reading or evaluating may be raw results (such as fluorescence intensity readings for each feature in one or more color channels) or may be processed results (such as those obtained by subtracting a background measurement, or by rejecting a reading for a feature which is below a predetermined threshold, normalizing the results, and/or forming conclusions based

on the pattern read from the array (such as whether or not a particular target sequence may have been accessible in the sample, or whether or not a pattern indicates a particular condition of an organism from which the sample came).

[00148] In one aspect, the present disclosure provides a method for determining an epigenetic landscape of a biological sample. In certain embodiments, the method comprises: (a) providing a biological sample obtained from a patient, said biological sample comprising morphologically intact nuclei; (b) contacting the morphologically intact nuclei to a transposase complex to produce a population of tagged DNA fragments representing accessible chromatin regions (ACRs) of the morphologically intact nuclei; (c) attaching a set of oligonucleotide primers to produce amplicon fragments; and (d) set of primers amplify the specifically targeted ACRs with qPCR master mix containing SYBR-green for quantitation of amplified DNA fragments. In certain embodiments, the method does not include sequencing, or hybridization of the tagged fragments or amplicons thereof.

[00149] In one aspect, the present disclosure provides a method for comparing epigenetic landscapes between a test sample and a reference sample. In certain embodiments, the method comprises: (a) analyzing morphologically intact nuclei from the test sample to produce a first epigenetic landscape; (b) analyzing morphologically intact nuclei from the reference sample to produce a second epigenetic landscape; and (c) comparing the first epigenetic landscape to the second epigenetic landscape. In certain embodiments, the test sample and the reference sample can be obtained from the same individual at different times (*e.g.*, before and after treatment). In other embodiments, the test sample and the reference sample can be obtained from different individuals (*e.g.*, a cancer patient and a subject without cancer; a cancer patient with treatment-resistant cancer and a cancer patient with treatment-sensitive cancer; or a cancer patient with an unknown diagnosis/prognosis and a cancer patient with treatment-resistant – or, alternatively, treatment-sensitive – cancer). In certain embodiments, the morphologically intact nuclei from the test sample and/or from the reference sample are analyzed according to a method described herein, such as by an ATAC-qPCRarray approach.

[00150] In one aspect, the present disclosure provides a method for identifying an epigenetic landscape characteristic of resistance to a cancer treatment modality. In certain embodiments, the method comprises (a) providing a first sample comprising cells from a treatment-resistant tumor (*e.g.*, a recurrent pancreatic ductal adenocarcinoma, where the recurrence is within one year of resection) and a second sample comprising non-cancerous cells or tumor cells from a treatment-sensitive tumor (*e.g.*, a non-recurrent pancreatic ductal adenocarcinoma or a late recurrent pancreatic ductal

adenocarcinoma, where the recurrence is beyond 2 and up to 5 years after resection); (b) identifying accessible chromatin regions (ACRs) in both samples; and (c) comparing the ACRs identified in the first sample to the ACRs identified in the second sample. In certain embodiments, the epigenetic landscape characteristic of resistance to treatment comprises one or more ACRs present in first sample and not present in the second sample and/or one or more ACRs present in second sample and not present in the first sample. In certain embodiments, the cancer is pancreatic cancer. Pancreatic cancer includes, for example, adenocarcinomas (tumors exhibiting glandular architecture) arising within the exocrine component of the pancreas and neuroendocrine carcinomas arising from islet cells. Pancreatic ductal adenocarcinoma (PDAC) is the most common form of pancreatic cancer. Other forms of pancreatic cancer include mucinous adenocarcinoma, acinic cell neoplasm, and neuroendocrine carcinoma. In certain embodiments, the treatment modality is selected from the group consisting of surgical resection, chemotherapy, radiation, immunotherapy, and a combination thereof.

7.2.1. ATAC-QPCR Array Methods for Determining a Prognostic Score

[00151] Described are methods for determining the prognostic score of a subject using ATAC-QPCR arrays. The prognostic score can be used to assess, determine or predict the subject's responsiveness to one or more treatment modalities, disease-free survival score, and/or likelihood of cancer recurrence for pancreatic cancer and/or other cancers.

[00152] In one aspect, described are methods for determining a prognostic score indicative of a subject's responsiveness to one or more treatment modalities or indicative of a duration of disease-free survival, the method comprising: (a) contacting a biological sample obtained from the subject with a transposase complex to produce a population of tagged DNA fragments representing accessible chromatin regions of intact nuclei or intact nucleosome structure, wherein the biological sample comprises pancreatic ductal adenocarcinoma cells having morphologically intact nuclei or intact nucleosomes; (b) hybridizing a set of targeting oligonucleotide probes to a specific region on the accessible chromatin regions to generate targeted accessible chromatin region fragments, wherein the targeting oligonucleotide probes specifically target differentially accessible chromatin regions, and wherein the targeting oligonucleotide probes comprise: (i) a first subset of oligonucleotide probes targeting accessible chromatin regions associated with a first phenotype, and (ii) a second subset of oligonucleotide probes targeting accessible chromatin regions associated with a second phenotype; (c) amplifying the targeted accessible chromatin region fragments obtained in (b) that are associated with the first phenotype and the second phenotype; and (d) determining a prognostic score based on

epigenetic signature values of the biological sample, wherein the prognostic score is determined based on a differential of a first epigenetic signature value and a second epigenetic signature value, and wherein the prognostic score is indicative of the subject's responsiveness to the one or more treatment modalities or indicative of a duration of disease-free survival.

[00153] In one aspect, described are methods of treating a subject having, or suspected of having, pancreatic ductal adenocarcinoma with one or more treatment modalities, the method comprising: (a) receiving a prognostic score indicative of the subject's responsiveness to one or more treatment modalities or indicative of a duration of disease-free survival, wherein the prognostic score is determined based on epigenetic signature values of a biological sample from the subject that comprises pancreatic ductal adenocarcinoma cells having morphologically intact nuclei or intact nucleosomes, the biological sample having been contacted with a transposase complex to produce a population of tagged DNA fragments representing accessible chromatin regions of the intact nuclei or intact nucleosome structure, wherein a set of targeting oligonucleotide probes were hybridized to a specific region on the accessible chromatin regions to generate targeted accessible chromatin region fragments, wherein the targeting oligonucleotide probes specifically target differentially accessible chromatin regions, wherein the prognostic score is determined based on a differential of a first epigenetic signature value and a second epigenetic signature value; and (b) treating the subject with the one or more treatment modalities based on the prognostic score.

[00154] The method can comprise collecting a biological sample from a subject having been diagnosed with a cancer (e.g., pancreatic cancer) or is at risk of having a cancer. In some embodiments, the biological sample is a tumor biopsy or surgically resected tumor specimen. In some embodiments, the biological sample comprises shredded cells from the subject such as epithelial cells or the subject's excreta (e.g., feces, saliva, sweat, earwax, mucus, urine). The biological sample can be collected by a physician, a surgeon, a healthcare provider, a laboratory technician or scientist. The biological sample may comprise pancreatic ductal adenocarcinoma cells. In some embodiments, the biological sample comprises treatment-naïve malignant cells obtained from a subject. In some embodiments, the biological sample comprises malignant cells from a subject who has been treated with one or more cancer therapies. In some embodiments, the biological sample is enriched for tumor cells. The enrichment can be achieved by contacting the biological sample with an agent (e.g., antibody-conjugated magnetic beads, EpCAM-conjugated magnetic beads) to isolate tumor cells from non-tumor cells in the biological sample to enrich the sample for tumor cells. In some embodiments, the agent is an EpCAM-conjugated magnetic beads. In some embodiments, the agent is an EpCAM-

conjugated non-magnetic beads such as one used in flow-cytometry assays or immunohistochemistry assays.

[00155] Morphologically intact nuclei or intact nucleosomes of the enriched tumor cells (e.g., pancreatic ductal adenocarcinoma cells) can be extracted from the biological sample. The extracted intact nuclei can be used to generate an ATAC-library using enzymatic-based or non-enzymatic-based fragmentation of the genomic DNA into fragments. In some embodiments, fragmenting and tagging the accessible chromatin regions (ACRs) comprise using enzymatic tagmentation such as using Tn transposase-based or restriction enzyme-based tagmentation. In some embodiments, fragmenting and tagging ACRs comprising using non-enzymatic tagmentation such as sonication, microfluidic shearing, or chemical cleavage (e.g., hydrogen peroxide, potassium permanganate). Example 2 in Section 8 illustrates an enzyme-based tagmentation method for generating ATAC libraries suitable for using the ATAC-qPCR array assay described herein. The ATAC-library can be used as the template for the ATAC-qPCR array assay.

[00156] The method may further comprise attaching a detectable label to the tagged DNA fragments to produce labeled fragments; and/or contacting the detectable labeled fragments to the set of targeting oligonucleotide probes. The method may further comprise quantifying the amount of amplified targeted accessible chromatin region fragments to obtain the first epigenetic signature value and the second epigenetic value. In some embodiments, the amplified targeted accessible chromatin region fragments are quantified by polymerase chain reaction (e.g., RT-PCR, qPCR), fluorometry, and/or gel electrophoresis. In some embodiments, quantification of the amplified targeted accessible chromatin region fragments does not involve sequencing the fragments.

[00157] In some embodiments, the set of targeting oligonucleotide probes are selected from any pair of oligonucleotide probes in Table 4. In some embodiments, the set of targeting oligonucleotide probes comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more pairs of oligonucleotide probes. In some embodiments, the set of targeting oligonucleotide probes are selected from any pair of oligonucleotide probes in Table 4. In some embodiments, at least 3 pairs of oligonucleotide probes are selected. In some embodiments, at least 8 pairs of oligonucleotide probes are selected. In some embodiments, at least 12 pairs of oligonucleotide probes are selected.

[00158] In some embodiments, the set of targeting oligonucleotide probes comprises no more than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 pairs of oligonucleotide probes. In some embodiments, the set of targeting oligonucleotide probes comprises no more than 3 pairs of

oligonucleotide probes. In some embodiments, the set of targeting oligonucleotide probes comprises no more than 8 pairs of oligonucleotide probes. In some embodiments, the set of targeting oligonucleotide probes comprises no more than 12 pairs of oligonucleotide probes.

[00159] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10. In some embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is about 12.

[00160] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis or poor prognosis is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10. In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis is about 3. In some embodiments, the set of targeting oligonucleotide probes required for effectively determining poor prognosis is about 8.

[00161] In some embodiments, the pair of targeting oligonucleotide probes comprise a nucleic acid sequence having a sequence of any one of SEQ ID NOs: 1-30. In some embodiments, the pair of targeting oligonucleotide probes comprise a nucleic acid sequence having a sequence having at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 99% identity to any one of SEQ ID NOs: 1-30.

[00162] In some embodiments, the set of targeting oligonucleotide probes comprises at least one set of probes targeting ARHGEF10, CLDN23, C12orf36, or SPATA4. In some embodiments, the set of targeting oligonucleotide probes comprises any two sets of probes targeting ARHGEF10, CLDN23, C12orf36, or SPATA4. In some embodiments, the set of targeting oligonucleotide probes comprises any three sets of probes targeting ARHGEF10, CLDN23, C12orf36, or SPATA4. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting ARHGEF10, CLDN23, C12orf36, SPATA4, or combinations thereof. In some embodiments, the set of targeting oligonucleotide probes comprises a set of probes targeting ARHGEF10, CLDN23, C12orf36, or SPATA4.

[00163] In some embodiments, the set of targeting oligonucleotide probes comprises at least one set of probes targeting MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV. In some embodiments, the set of targeting oligonucleotide probes comprises at least two sets of probes targeting MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV. In some embodiments, the set of targeting oligonucleotide probes comprises at least three sets of

probes targeting MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV. In some embodiments, the set of targeting oligonucleotide probes comprises at least 4, 5, 6, 7, or 8 sets of probes targeting MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, ITGAV, or combinations thereof. In some embodiments, the set of targeting oligonucleotide probes comprises a probe targeting MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV.

[00164] In some embodiments, the set of targeting oligonucleotide probes comprises at least one set of probes targeting GTF3C6, LINC01703, C1orf131, or XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises at least two sets of probes targeting GTF3C6, LINC01703, C1orf131, or XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises at least three sets of probes targeting GTF3C6, LINC01703, C1orf131, or XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting GTF3C6, LINC01703, C1orf131, XRCC2, or combinations thereof. In some embodiments, the set of targeting oligonucleotide probes comprises a set of probes targeting GTF3C6, LINC01703, C1orf131, or XRCC2.

[00165] In some embodiments, the set of targeting oligonucleotide probes comprises at least one set of probes targeting ARHGEF10, CLDN23, C12orf36, and SPATA4, at least one of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, or RN7SL300P, and at least one set of probes targeting GTF3C6, LINC01703, C1orf131, or XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises at least two sets of probes targeting ARHGEF10, CLDN23, C12orf36, and SPATA4, at least two of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, or RN7SL300P, and at least two sets of probes targeting GTF3C6, LINC01703, C1orf131, or XRCC2.

[00166] In some embodiments, the set of targeting oligonucleotide probes comprises at least one set of probes targeting ARHGEF10, CLDN23, C12orf36, SPATA4, MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, GTF3C6, LINC01703, C1orf131, XRCC2, or combinations thereof. In some embodiments, the set of targeting oligonucleotide probes comprises any one set of probes targeting ARHGEF10, CLDN23, C12orf36, SPATA4, MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, GTF3C6, LINC01703, C1orf131, XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises a set of probes targeting

ARHGEF10, CLDN23, C12orf36, SPATA4, MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, GTF3C6, LINC01703, C1orf131, XRCC2.

[00167] In some embodiments, the accessible chromatin regions are selected from any one of the accessible chromatin regions in FIG. 9A, FIG. 9B, and/or Table 3. In some embodiments, the accessible chromatin regions are selected from any one of the accessible chromatin regions in Table 3. In some embodiments, at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 accessible chromatin regions are selected from any one of the accessible chromatin regions in FIG. 9A, FIG. 9B, and/or Table 3. In some embodiments, at least 3 accessible chromatin regions are selected from any one of the accessible chromatin regions in FIG. 9A, FIG. 9B, and/or Table 3. In some embodiments, at least 8 accessible chromatin regions are selected from any one of the accessible chromatin regions in FIG. 9A, FIG. 9B, and/or Table 3. In some embodiments, at least 12 accessible chromatin regions are selected from any one of the accessible chromatin regions in FIG. 9A, FIG. 9B, and/or Table 3.

[00168] In some embodiments, the method further comprising the step of comparing the first epigenetic signature value to the second epigenetic signature value to obtain a differential value.

[00169] In some embodiments, the first epigenetic signature value is the median value of a set of accessible chromatin regions indicating a poor prognosis. In some embodiments, the median value of a set of accessible chromatin regions indicating a poor prognosis is the median value of at least 3 replications of ATAC-qPCR array analyses (e.g., the median Ct value) of the accessible chromatin regions selected from at least 1, 2, 3, 4, 5, 6, 7, or 8 of RN7SL, CNBP, MAP2K2, ITGAV, PPAP2B, FIG4, PAPL, and TTC19. In some embodiments, the accessible chromatin regions are selected from RN7SL, CNBP, MAP2K2, ITGAV, PPAP2B, FIG4, PAPL, TTC19, and/or combinations thereof.

[00170] In some embodiments, the second epigenetic signature value is the median value of a set of accessible chromatin regions indicating a good prognosis. In some embodiments, the median value of a set of accessible chromatin regions indicating a good prognosis is the median value of at least 3 replications of ATAC-qPCR array analyses (e.g., the median Ct value) of the accessible chromatin region selected from at least 1, 2, 3, or 4 of CLDN23, SPATA4, ARHGEF-10, and C12orf36. In some embodiments, the accessible chromatin regions are selected from CLDN23, SPATA4, ARHGEF-10, C12orf36, and/or combinations thereof.

[00171] In some embodiments, the method further comprising normalizing the differential value with at least one of a positive control epigenetic signature value and one of a negative control epigenetic signature value to obtain the prognostic score. In some embodiments, the control epigenetic signature value is determined by obtaining the median value of a set of accessible chromatin regions indicating the median value of at least 3 replications of ATAC-qPCR array analyses (e.g., the median Ct value) of the accessible chromatin regions selected from at least 1, 2, 3, or 4 of GTF3C6, LINC01703, C1orf131, and XRCC2. In some embodiments, the accessible chromatin regions are selected from GTF3C6, LINC01703, C1orf131, XRCC2, and/or combinations thereof.

[00172] In some embodiments, the prognostic score is at least 0.6 for determining a subject has a good prognosis or responsiveness to one or more treatment modalities described herein. In some embodiments, the prognostic score is less than 0.6 for determining a subject has a poor prognosis or responsiveness to one or more treatment modalities described herein.

[00173] In some embodiments, the method further comprising detecting nuclear localization of at least one of a transcription factor selected from any one of the transcription factors in Tables 2A and 2B. In some embodiments, the method further comprising detecting nuclear localization of at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 15, 20, 25, 30, 35, 40, or 50 transcription factors selected from any one of the transcription factors in Tables 2A and 2B.

[00174] In some embodiments, the transcription factors are selected from ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFH3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.

[00175] In some embodiments, the transcription factors are selected from at least 2, 3, 4, 5, 6, 7, 8, 9, or 10 of transcription factors ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL,

GATA2, GATA1, HMBOX1, NRF1, ZFH3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.

[00176] In some embodiments, the transcription factors are selected from ZKSCAN1A, HNF1B, or a combination thereof.

[00177] In some embodiments, the method further comprises predicting a long duration of disease-free survival when the second epigenetic signature value is significantly higher than the second epigenetic signature value and/or predicting a short duration of disease-free survival when the first epigenetic signature value is significantly higher than the second epigenetic value.

[00178] In some embodiments, the first epigenetic signature value indicates a first phenotype.

[00179] In some embodiments, the first phenotype is recurrence of a cancer within 6 months, or 1, 2, 3, 4, or 5 years of surgical resection. In some embodiments, the first phenotype is recurrence of a cancer within one year of surgical resection.

[00180] In some embodiments, the first phenotype is recurrence of a cancer within one year of surgical resection. In some embodiments, the first phenotype is recurrence of a cancer within 11 months, 10 months, 9 months, 8 months, 7 months, 6 months, 5 months, 4 months, 3 months, 2 months or 1 month of surgical resection.

[00181] In some embodiments, the first phenotype is having a median disease-free survival of less than 5, 4, 2, 3, 1 or less years. In some embodiments, the second phenotype is having a median disease-free survival of less than 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or less months. In some embodiments, the second phenotype is having a median disease-free survival of less than 350, 300, 250, 200, 150, 100, 50, 10, or less days. In some embodiments, the second phenotype is having a median disease-free survival of less than 50 days.

[00182] In some embodiments, the first phenotype is having a median disease-free survival of between 1 to 350 days, between 50-300 days, between 10-100 days, or between 40 to 250 days.

[00183] In some embodiments, the second epigenetic signature value indicates a second phenotype.

[00184] In some embodiments, the second phenotype is non-recurrence of a cancer within 6 months, or 1, 2, 3, 4, or 5 years of surgical resection. In some embodiments, the second phenotype is non-recurrence of a cancer within one year of surgical resection.

[00185] In some embodiments, the second phenotype is non-recurrence of a cancer within one year of surgical resection. In some embodiments, the second phenotype is non-recurrence of a cancer within 11 months, 10 months, 9 months, 8 months, 7 months, 6 months, 5 months, 4 months, 3 months, 2 months or 1 month of surgical resection.

[00186] In some embodiments, the second phenotype is having a median disease-free survival (DFS) of at least of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more years.

[00187] In some embodiments, the second phenotype is having a median disease-free survival (DFS) of at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, or more days.

[00188] In some embodiments, the second phenotype is having a median disease-free survival (DFS) of between 50 to 1500 days, between 100 to 1000 days, between 300 to 800 days, between 200 to 500 days, or between 400 to 600 days. In some embodiments, the first phenotype is having a median disease-free survival of at least 350 days.

[00189] In some embodiments, the first phenotype is non-responder to a cancer therapy. In some embodiments, the second phenotype is responder to a cancer therapy. In some embodiments, the cancer therapy is selected from chemotherapy, immunotherapy, radiation, or combinations thereof.

[00190] In some embodiments, the biological sample comprises treatment-naïve malignant cells obtained from a subject. In some embodiments, the subject is a treatment naïve patient who has not received the one or more treatment modalities for a cancer such as pancreatic or other cancers. In some embodiments, the subject has not been diagnosed with a cancer such as pancreatic or other cancers.

[00191] In some embodiments, the subject is under treatment or has been treated with the one or more treatment modalities for a cancer such as pancreatic or other cancers.

[00192] In some embodiments, the one or more treatment modalities are selected from resecting cancerous tissue, neo-adjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, an epigenetic drug, or combinations thereof. In some embodiments, the epigenetic drug is selected from DNMT inhibitor, an HDAC inhibitor, an EZH2 inhibitor, or combinations thereof. In some embodiments, the DNMT inhibitor is azacytidine or decitabine. In some embodiments, the HDAC inhibitor is vorinostat or romidepsin.

[00193] In some embodiments, the neo-adjuvant chemotherapy and/or adjuvant chemotherapy is selected from gemcitabine, nab-paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, leucovorin, capecitabine, cisplatin, or combinations thereof.

[00194] In some embodiments, the biological sample is selected from a tumor biopsy or surgically resected tumor specimen.

[00195] In some embodiments, the method does not include sequencing the tagged fragments or amplicons thereof. In some embodiments, obtaining the targeted accessible chromatin region fragments does not include the step of sequencing the tagged fragments or amplicons thereof.

[00196] In some embodiments, the amplified targeted accessible chromatin fragments comprise a mean size of about 50 bp to about 1100 bp, about 100 bp to about 350 bp, about 150bp to about 800 bp, about 80 bp to about 150 bp, or about 150 bp to about 400 bp. In some embodiments, the amplified targeted accessible chromatin fragments comprise a mean size of 80 bp, about 100 bp, about 120 bp, about 150 bp, about 180 bp, about 200 bp, about 250 bp, about 300 bp, about 400 bp, about 500 bp, about 600 bp, about 700 bp, about 800 bp, about 900 bp, about 1000 bp, about 1100 bp, or longer. In some embodiments, the amplified targeted accessible chromatin fragments comprise a mean size of about 120 bp.

[00197] In accordance with any one of the embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.

[00198] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is about 12.

[00199] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis or poor prognosis is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.

[00200] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis is about 3.

[00201] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining poor prognosis is about 8.

[00202] In some embodiments, the method monitors patients with pancreatic cancer who had undergone upfront surgery followed by Gemcitabine/ Nab-Paclitaxel adjuvant chemotherapy. These patients are monitored for a median follow-up time of at least 1, 2, 3, 4, 5 or more years post-surgery. FIG. 8 shows the Kaplan-Meier graph showing patients with good prognosis and poor prognosis.

[00203] In some embodiments, the patients are monitored for 4.15 years post-surgery. Patients who show a median disease-free survival (DFS) of at least 100, 200, 300, 400, 500, 600, 700, 800, 900, 1000, 1200, 1400, 1600, 1800, 2000, or more days are determined as having good prognosis. In some embodiments, patients having good prognosis have a median DFS of between about 1000 days to 1800 days, for example, ranging from 1234 days to 1645 days. In some embodiments, patients having a good prognosis have a median DFS of 1478 days.

[00204] In some embodiments, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 99%, or more of patients having good prognosis have a median DFS of more than 400 days, 800 days, 1200 days, 1600 days, or more. In some embodiments, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 99%, or more of patients having a good prognosis have a median DFS of between 400 to 1600 days, 1200 to 1500 days, or 600 to 1400 days. In some embodiments, at least 75% of patients having a good prognosis have a median DFS of about 1400 days.

[00205] In some embodiments, patients predicted with a good prognosis have a median DFS of at least 400 days, 800 days, 1200 days, 1600 days, or more. In some embodiments, patients predicted with a good prognosis have a median DFS of between 400 to 1600 days, 1200 to 1500 days, or 600 to 1400 days. In some embodiments, patients predicted with a good prognosis have a median DFS of about 1478 days.

[00206] Patients who show a median disease-free survival (DFS) of less than 500, 400, 300, 200, 100, 50, 20, or 10 days are determined as having a poor prognosis. In some embodiments, patients having poor prognosis have a median DFS of between 30 days to 300 days, for example, ranging from 36 to 207 days. In some embodiments, patients having poor prognosis have a median DFS of 47 days.

[00207] In some embodiments, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 99%, or more of patients having poor prognosis have a median DFS of less than 400 days, 200 days, 100 days, 50 days, or less. In some embodiments, at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%,

at least 70%, at least 80%, at least 90%, at least 99%, or more of patients having a poor prognosis have a median DFS of between 10 to 400 days, 50 to 200 days, or 10 to 50 days. In some embodiments, at least 25% of patients having a poor prognosis have a median DFS of about 47 days.

[00208] In some embodiments, patients predicted with a poor prognosis have a median DFS of 400 days, 200 days, 100 days, 50 days, or less. In some embodiments, patients predicted with a poor prognosis have a median DFS of between 10 to 400 days, 50 to 200 days, or 10 to 50 days. In some embodiments, patients predicted with a poor prognosis have a median DFS of about 47 days

[00209] The relative accessibility of the differentially accessible chromatin regions (the solid line indicates good prognosis and the broken line indicates poor prognosis, normalized with the control) is estimated by 2^{-dCt} method in each patient by qPCR analyses of the individual ATAC-libraries prepared from them. The dCt values for each target region can be calculated as below:

$$dCt = Ct \text{ values of the differential (blue or red) regions} - \text{Geometric mean } Ct \text{ values of the control (green) regions}$$

[00210] FIGs. 9A and 9B show the results of ATAC-qPCR analysis of 11 target regions using 4 control regions for normalization. The relative quantitation of blue and red regions in each individual patient were shown by bar plot, where the open bars represented the blue (good prognosis) target regions and the striped bars represented the red (poor prognosis) target regions.

[00211] The Prognostic scores can be calculated using the ATAC-qPCR analytical methods as displayed in the formula below:

Prognostic score (PS) by ATAC-qPCR array = 2^{-dCt} of blue regions - 2^{-dCt} of red regions

[00212] As an example, FIG. 9A shows Patient PT35 having a median DFS of 1478 days. PT35 has high 2^{-dCt} values of good prognosis epigenetic signature values of accessible chromatin regions (e.g., CLDN23, SPATA4, and ARHGEF10), which have 2^{-dCt} values of between about 0.6 to about 3.5. PT35 has low 2^{-dCt} values of poor prognosis epigenetic signature values of accessible chromatin regions (e.g., RN7SL, CNBP, MAP2K2, ITGAV, PPAP2B, FIG4, PAPL, and TTC19), which have 2^{-dCt} values of between about 0.01 to about 0.2. For example, the normalized differential values of CLDN23 and MAP2K2 is about 0.6 to about 0.2, indicating a prognostic score (PS) of 0.4. The normalized differential value of SPATA4 to MAP2K2 is about 1 to about 0.2, indicating a PS of 0.8. The normalized differential value of ARHGEF10 and MAP2K2 is about 3.2 to about 0.2, indicating a PS of 2.8. Based on the formula, PT35 has a prognostic score of 0.8 and 2.8, which is higher than

0.6, when comparing the $2^{\Delta\text{dCt}}$ values of a good prognosis epigenetic signature value (e.g., SPATA4, and ARHGEF10) with a poor prognosis score (e.g., MAP2K2). As another example, an average of the normalized differential values of good prognosis epigenetic signature values of accessible chromatin regions including CLDN23, SPATA4, and ARHGEF10 is compared to an average of the normalized differential values of poor prognosis epigenetic signature values of accessible chromatin regions including RN7SL, CNBP, MAP2K2, ITGAV, PPAP2B, FIG4, PAPL, and TTC19 to determine a prognostic score. For illustration purposes, the average of the normalized differential values of good prognosis epigenetic signature values of CLDN23, SPATA4, and ARHGEF10 is about 1.67, and the average of the normalized differential values of good prognosis epigenetic signature values of RN7SL, CNBP, MAP2K2, ITGAV, PPAP2B, FIG4, PAPL, and TTC19 is about 0.12, giving a prognostic score of 1.55, which is higher than 0.6.

[00213] FIG. 9B shows Patient PT18 having a median DFS of 113. PT18 has $2^{\Delta\text{dCt}}$ values between about 0.15 to about 0.4 of good prognosis epigenetic signature values of accessible chromatin regions (e.g., CLDN23, SPATA4, and ARHGEF10), and has $2^{\Delta\text{dCt}}$ values between about 0.15 to about 0.3 of poor prognosis epigenetic signature values of accessible chromatin regions (e.g., RN7SL, CNBP, MAP2K2, ITGAV, PPAP2B, FIG4, PAPL, and TTC19). For example, the normalized differential value of CLDN23 and MAP2K2 is about 0.18 to about 0.28, indicating a prognostic score (PS) of -0.1. The normalized differential value of SPATA4 and MAP2K2 is about 0.25 to about 0.28, indicating a prognostic score (PS) of -0.03. The normalized differential value of ARHGEF10 and MAP2K2 is about 0.38 to about 0.28, indicating a prognostic score (PS) of 0.1. Based on the formula, PT18 has a prognostic score of -0.1, -0.03, and 0.1, which is lower than 0.6, when comparing the $2^{\Delta\text{dCt}}$ values of a good prognosis epigenetic signature value (e.g., CLDN23, SPATA4, and ARHGEF10) with a poor prognosis score (e.g., MAP2K2). As another example, an average of the normalized differential values of good prognosis epigenetic signature values of accessible chromatin regions including CLDN23, SPATA4, and ARHGEF10 is compared to an average of the normalized differential values of poor prognosis epigenetic signature values of accessible chromatin regions including RN7SL, CNBP, MAP2K2, ITGAV, PPAP2B, FIG4, PAPL, and TTC19 to determine a prognostic score. For illustration purposes, the average of the normalized differential values of good prognosis epigenetic signature values of CLDN23, SPATA4, and ARHGEF10 is about 0.27, and the average of the normalized differential values of good prognosis epigenetic signature values of RN7SL, CNBP, MAP2K2, ITGAV, PPAP2B, FIG4, PAPL, and TTC19 is about 0.21, giving a prognostic score of 0.06, which is lower than 0.6.

[00214] Using the formula described above, the individualized PS for each patient can be calculated and the PS of good and poor prognosis groups can be analyzed. The box plot as displayed in **FIG. 10** demonstrated a statistically significant difference (t test $p=0.034$) of PS between the 7 good and 7 poor prognosis patients. Open bar represents good prognosis. Stripped bar represents poor prognosis.

[00215] In some embodiments, a prognostic score of between 0.3 to 2, between 0.5 to 1.5, or between 0.6 to 1.3 provides the prediction for a good prognosis. In some embodiments, a prognostic score of about 0.3, 0.6, 0.9, 1.2, 1.5, 1.8, or above provides the prediction for a good prognosis. In some embodiments, a prognostic score of above 0.6 provides the prediction for a good prognosis.

[00216] In some embodiments, a prognostic score of between 0.1 to 1, between 0.2 to 0.6, or between 0.4 to 0.8 provides the prediction for a poor prognosis. In some embodiments, a prognostic score of about 1, 0.9, 0.8, 0.7, 0.6, 0.5, 0.4, 0.3, 0.2, 0.1 or less provides the prediction for a poor prognosis. In some embodiments, a prognostic score of less than 0.6 provides the prediction for a poor prognosis.

[00217] The method can successfully determine a set of targeting oligonucleotide probes required for effectively determining a reliable prognostic score. In some embodiments, the set of targeting oligonucleotide probes required can be less than 100, or as few as 12 probes. The set of targeting oligonucleotide probes required for effectively determining good prognosis can be as few as 3 probes, and the set of targeting oligonucleotide probes required for effectively determining poor prognosis can be as few as 8 probes. The method using ATAC-qPCR array is a robust, reliable, and cost-effective approach for determining prognostic score of a patient having, or at risk of developing pancreatic cancer. Such information is critical for the selection of treatment modalities, which can enhance the subject's likelihood of disease-free survival.

7.3 Diagnosis, Prognosis, and Treatment of Cancer

[00218] In one aspect, the present disclosure provides a diagnostic or prognostic method. In certain embodiments, the diagnostic or prognostic method may distinguish between treatment-resistant and treatment-sensitive cancers. In certain embodiments, the diagnostic or prognostic method may distinguish between rapidly recurrent and non-recurrent tumors. In some such embodiments, the tumors are pancreatic tumors, such as pancreatic ductal adenocarcinoma.

[00219] In certain embodiments, the diagnostic or prognostic method comprises determining a epigenetic landscape from a biological sample obtained from a patient, wherein the epigenetic landscape comprises at least two, alternatively at least five, at least ten, at least twenty, at least thirty, at least forty, at least fifty, at least one hundred, at least two hundred, at least three hundred, at least four hundred, at least five hundred, at least six hundred, at least seven hundred, at least eight hundred, at least nine hundred, or at least one thousand chromatin regions selected from the list of chromatin regions in Table 1 and/or Table 2; and providing a diagnosis or prognosis based on the determination. In typical embodiments, the diagnostic or prognostic method comprises determining a epigenetic landscape comprising no more than 100 open chromatin regions in Table 1 and/or Table 2.

[00220] In one aspect, the present disclosure provides a method for treating a disease or condition such as cancer, particularly pancreatic cancer. In certain embodiments, the method comprises performing surgical resection to remove a pancreatic ductal adenocarcinoma from a patient, wherein prior to said resection a biological sample from the patient has been tested to determine an epigenetic landscape of the biological sample. In some such embodiments, the epigenetic landscape comprises a plurality of pre-selected differentially accessible chromatin regions and the plurality of pre-selected differentially accessible chromatin regions comprise at least two, alternatively at least five, at least ten, at least twenty, at least thirty, at least forty, at least fifty, at least one hundred, at least two hundred, at least three hundred, at least four hundred, at least five hundred, at least six hundred, at least seven hundred, at least eight hundred, at least nine hundred, or at least one thousand chromatin regions selected from the list of chromatin regions in Table 1 and/or Table 2, which provides a signature of >1000 loci that were differentially accessible between recurrent (disease free survival (DFS) < 1 year) and non-recurrent patients (DFS > 1 year). In typical embodiments, the diagnostic or prognostic method comprises determining a epigenetic landscape comprising no more than 100 differentially accessible open chromatin regions in Table 1 and/or Table 2. In certain embodiments, the method comprises performing surgical resection to remove a pancreatic ductal adenocarcinoma from a patient, wherein prior to said resection a biological sample from the patient has been tested to determine nuclear localization of one or more transcription factors.

[00221] In one aspect, the present disclosure provides a method for treating a disease or condition such as cancer, particularly pancreatic cancer. In certain embodiments, the method comprises administering a drug to the patient, wherein prior to administering the drug, a biological sample from the patient has been tested to determine an epigenetic landscape of the biological sample.

[00222] In certain embodiments, the patient is identified as likely being a non-responder to a treatment modality. In some such embodiments, the treatment modality is surgical resection with or without adjuvant chemotherapy. In certain embodiments, the patient is identified as having a tumor likely to recur within one year following surgical resection and adjuvant chemotherapy. In some such embodiments, the tumor is a pancreatic ductal adenocarcinoma.

[00223] In certain embodiments, the epigenetic landscape comprises a plurality of pre-selected differentially accessible chromatin regions and the plurality of pre-selected differentially accessible chromatin regions comprise at least two, alternatively at least five, at least ten, at least twenty, at least thirty, at least forty, at least fifty, at least one hundred, at least two hundred, at least three hundred, at least four hundred, at least five hundred, at least six hundred, at least seven hundred, at least eight hundred, at least nine hundred, or at least one thousand chromatin regions selected from the list of chromatin regions in Table 1, which provides a signature of >1000 loci that were differentially accessible between recurrent (disease-free survival (DFS) < 1 year) and non-recurrent patients (DFS > 1 year). In typical embodiments, the epigenetic landscape comprises no more than 100 pre-selected differentially accessible chromatin regions in Table 1 and/or Table 2.

[00224] In certain embodiments, the method comprises administering the epigenetic drug to the patient, wherein prior to said administration a biological sample from the patient has been tested to determine nuclear localization of one or more transcription factors.

[00225] In one aspect, the present disclosure provides a method for treating cancer in a patient in need thereof. In certain embodiments, the method comprises (a) assessing if the patient is likely to be a responder or a non-responder to a first treatment modality by determining or having determined an epigenetic landscape of a biological sample obtained from the cancer patient; and (b) treating the cancer patient with a second treatment modality if the patient is determined to be a likely non-responder to the first treatment modality.

7.3.1. Prognosis of Cancer

[00226] Described herein are methods for determining a prognosis of a cancer. The method can comprise determining and/or providing a prognostic score indicative of a subject's responsiveness to one or more treatment modalities or indicative of a duration of disease-free survival as described in Section 7.2.1, and Examples 2, 5, 6, and 7. In some embodiments, the method further comprises determining or providing a first epigenetic signature value, a second epigenetic signature value, a good

prognosis report, a poor prognosis report, a disease-free survival score, a report of a likelihood of cancer recurrence or non-recurrence, and/or a prediction of treatment modality responsiveness.

[00227] In some embodiments, prognosis of a cancer comprises determining a first epigenetic signature value and a second epigenetic signature value. The first epigenetic signature value indicates a first phenotype, which is a poor prognosis of the cancer. The second epigenetic signature value indicates a second phenotype, which is a good prognosis of the cancer.

[00228] In some embodiments, prognosis of the cancer comprises using the first and second epigenetic signature values to determine the likelihood of recurrence or non-recurrence of a cancer. For example, a high first epigenetic signature value may indicate a higher likelihood of recurrence of the cancer within a year or less. A high second epigenetic signature value may indicate a lower likelihood of recurrence of the cancer within a year or less.

[00229] The differential of the first epigenetic signature value and the second epigenetic signature value can be normalized with a control epigenetic signature value to determine a prognostic score. For example, a prognostic score of less than 0.6 indicates recurrence of the cancer or poor responsiveness (e.g., non-responder) to one or more cancer treatment modalities. Conversely, a prognostic score of higher than 0.6 indicates non-recurrence of the cancer or good responsiveness (e.g., responder) to one or more cancer treatment modalities.

[00230] In some embodiments, the one or more treatment modalities are selected from resecting cancerous tissue, neo-adjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, an epigenetic drug, or combinations thereof. In some embodiments, the epigenetic drug is selected from DNMT inhibitor, an HDAC inhibitor, an EZH2 inhibitor, or combinations thereof. In some embodiments, the DNMT inhibitor is azacytidine or decitabine. In some embodiments, the HDAC inhibitor is vorinostat or romidepsin. In some embodiments, the neo-adjuvant chemotherapy and/or adjuvant chemotherapy is selected from gemcitabine, nab-paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, leucovorin, capecitabine, cisplatin, or combinations thereof.

[00231] In some embodiments, the prognostic score is used to determine the disease-free survival (DFS) of the subject. For example, a subject having a prognostic score of higher than 0.6 may have a median DFS of at least of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more years, or at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, or more days. FIG. 6 shows subjects having a

median DFS of 592 days are determined to have a good prognosis, and subjects having a median DFS of 325.5 days are determined to have a poor prognosis.

[00232] The prognostic score can be determined by assessing the differential values of good prognosis and poor prognosis by obtaining the epigenetic signature values of accessible chromatin regions as shown in FIGs. 9A and 9B, and/or Table 3. In some embodiments, the prognostic score can be determined by assessing the differential values of good prognosis and poor prognosis obtaining the epigenetic signature values of less than 12, 8, 4, or 3 accessible chromatin regions as shown in FIGs. 9A and 9B, and/or Table 3. Using the accessible chromatin regions in Table 3 to determine the prognostic score, FIG. 8A subjects having a median DFS of 1478 days are determined to have a good prognosis, and subjects having a median DFS of 47 days are determined to have a poor prognosis.

[00233] In some embodiments, the prognostic score is determined or provided by a physician, a surgeon, a healthcare provider, a laboratory technician or scientist, or a data analyst.

7.3.2. Treatment of Cancer

[00234] Described herein are methods for determining treatment modalities for a cancer such as pancreatic or other cancers. The method comprises determining and/or receiving a prognostic score indicative of a subject's responsiveness to one or more treatment modalities or indicative of a duration of disease-free survival and treating the subject with the one or more treatment modalities based on the prognostic score. In some embodiments, the prognostic score is determined using the ATAC-array qPCR assays described in Section 7.2.1, Section 7.3.1, and Examples 2, 5, 6, and 7. In some embodiments, the method further comprises determining or receiving a first epigenetic signature value, a second epigenetic signature value, a good prognosis report, a poor prognosis report, a disease-free survival score, a report of a likelihood of cancer recurrence or non-recurrence, and/or or prediction of treatment modality responsiveness.

[00235] A subject having a prognostic score higher than 0.6, a good prognosis report, indication of non-recurrence, or a high disease-free survival score may be prescribed or administered with one or more treatment modalities. Conversely, a subject having a prognostic score lower than 0.6, a poor prognosis report, indication of recurrence, or a low disease-free survival score may be advised to have no further treatment modalities.

[00236] In some embodiments, the one or more treatment modalities are selected from resecting cancerous tissue, neo-adjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, an epigenetic

drug, or combinations thereof. In some embodiments, the epigenetic drug is selected from DNMT inhibitor, an HDAC inhibitor, an EZH2 inhibitor, or combinations thereof. In some embodiments, the DNMT inhibitor is azacytidine or decitabine. In some embodiments, the HDAC inhibitor is vorinostat or romidepsin. In some embodiments, the neo-adjuvant chemotherapy and/or adjuvant chemotherapy is selected from gemcitabine, nab-paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, leucovorin, capecitabine, cisplatin, or combinations thereof.

[00237] In some embodiments, the treatment modalities are prescribed or administered by a physician, a surgeon, a healthcare provider, a laboratory technician or scientist, or a data analyst.

In some embodiments, the subject is a treatment naïve patient who has not received the one or more treatment modalities for a cancer such as pancreatic or other cancers. In some embodiments, the subject has not been diagnosed with a cancer such as pancreatic or other cancers. In some embodiments, the subject is under treatment or has been treated with the one or more treatment modalities for a cancer such as pancreatic or other cancers.

7.4 Kits

[00238] In one aspect, described are kits for determining an epigenetic landscape associated with a specific phenotypic trait of a biological sample, the kit comprising:

- (d) an array configured to detect targeted accessible chromatin region fragments obtained from the biological sample, wherein the array comprises a panel of sets of targeting oligonucleotide probes specifically targeting differentially accessible chromatin regions;
- (e) reagents; and
- (f) instructions for amplifying and quantifying the targeted accessible chromatin region fragments to obtain a first epigenetic signature value and a second epigenetic value.

[00239] In one aspect, described are kits for determining an epigenetic landscape associated with a specific phenotypic trait of a biological sample, the kit comprising:

- (d) one or more sets of targeting oligonucleotide probes for detect targeted accessible chromatin region fragments obtained from the biological sample, wherein the targeting oligonucleotide probes specifically target and amplify differentially accessible chromatin regions to generate one or more targeted accessible chromatin region fragments;
- (e) reagents; and

- (f) instructions for amplifying and quantifying the targeted accessible chromatin region fragments to obtain a first epigenetic signature value and a second epigenetic value.

[00240] In some embodiments, the targeting oligonucleotide probes are provided in a panel. In some embodiments, the panel of targeting oligonucleotide probes is arranged as described in FIG. 4A or 4B.

[00241] In some embodiments, the targeting oligonucleotide probes are provided in a 96-well plate. In some embodiments, the targeting oligonucleotide probes are provided in a 384-well plate. In some embodiments, the targeting oligonucleotide probes are provided in one or more individual containers, e.g., an Eppendorf tube.

[00242] In some embodiments, the biological sample comprises pancreatic ductal adenocarcinoma cells having morphologically intact nuclei or intact nucleosome (histone-DNA) structure.

[00243] In some embodiments, the kit further comprises reagents and instructions for obtaining the biological sample by contacting the morphologically intact nuclei or intact nucleosome (histone-DNA) structure to a transposase complex to produce a population of tagged DNA fragments representing the targeted accessible chromatin region fragments.

[00244] In some embodiments, the pair of targeting oligonucleotide probes comprise a nucleic acid sequence having a sequence of any one of SEQ ID NOs: 1-30. In some embodiments, the pair of targeting oligonucleotide probes comprise a nucleic acid sequence having a sequence having at least 10%, at least 20%, at least 30%, at least 40%, at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, or at least 99% identity to any one of SEQ ID NOs: 1-30.

[00245] In some embodiments, the set of targeting oligonucleotide probes comprises at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, or more pairs of oligonucleotide probes. In some embodiments, the set of targeting oligonucleotide probes are selected from any pair of oligonucleotide probes in Table 4. In some embodiments, at least 3 pairs of oligonucleotide probes are selected. In some embodiments, at least 8 pairs of oligonucleotide probes are selected. In some embodiments, at least 12 pairs of oligonucleotide probes are selected.

[00246] In some embodiments, the set of targeting oligonucleotide probes comprises no more than 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, or 20 pairs of oligonucleotide probes. In some embodiments, the set of targeting oligonucleotide probes comprises no more than 3 pairs of

oligonucleotide probes. In some embodiments, the set of targeting oligonucleotide probes comprises no more than 8 pairs of oligonucleotide probes. In some embodiments, the set of targeting oligonucleotide probes comprises no more than 12 pairs of oligonucleotide probes.

[00247] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10. In some embodiments, the set of targeting oligonucleotide probes required for effectively determining the prognostic score is about 12.

[00248] In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis or poor prognosis is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10. In some embodiments, the set of targeting oligonucleotide probes required for effectively determining good prognosis is about 3. In some embodiments, the set of targeting oligonucleotide probes required for effectively determining poor prognosis is about 8.

[00249] In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of ARHGEF10, CLDN23, C12orf36, or SPATA4. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting any two of ARHGEF10, CLDN23, C12orf36, or SPATA4. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting any three of ARHGEF10, CLDN23, C12orf36, or SPATA4. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting ARHGEF10, CLDN23, C12orf36, SPATA4, or combinations thereof. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting ARHGEF10, CLDN23, C12orf36, or SPATA4.

[00250] In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least two of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least three of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least 4, 5, 6, 7, or 8 of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, ITGAV, or combinations thereof. In some embodiments, the set

of targeting oligonucleotide probes comprises probes targeting MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, or ITGAV.

[00251] In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of GTF3C6, LINC01703, C1orf131, or XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least two of GTF3C6, LINC01703, C1orf131, or XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least three of GTF3C6, LINC01703, C1orf131, or XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of GTF3C6, LINC01703, C1orf131, XRCC2, or combinations thereof. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting GTF3C6, LINC01703, C1orf131, or XRCC2.

[00252] In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of ARHGEF10, CLDN23, C12orf36, and SPATA4, at least one of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, or RN7SL300P, and at least one of GTF3C6, LINC01703, C1orf131, or XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least two of ARHGEF10, CLDN23, C12orf36, and SPATA4, at least two of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, or RN7SL300P, and at least two of GTF3C6, LINC01703, C1orf131, or XRCC2.

[00253] In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting at least one of ARHGEF10, CLDN23, C12orf36, SPATA4, MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, GTF3C6, LINC01703, C1orf131, XRCC2, or combinations thereof. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting any one of ARHGEF10, CLDN23, C12orf36, SPATA4, MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, GTF3C6, LINC01703, C1orf131, XRCC2. In some embodiments, the set of targeting oligonucleotide probes comprises probes targeting ARHGEF10, CLDN23, C12orf36, SPATA4, MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, GTF3C6, LINC01703, C1orf131, XRCC2.

[00254] In some embodiments, the kit further comprises reagents and instructions for enriching the biological sample obtained from the subject for tumor cells.

[00255] In some embodiments, the reagents comprise antibody-conjugated magnetic beads, EpCAM-conjugated magnetic beads, or a combination thereof to isolate tumor cells from non-tumor

cells in the biological sample. The enrichment can be achieved by contacting the biological sample with an agent (e.g., antibody-conjugated magnetic beads, EpCAM-conjugated magnetic beads) to isolate tumor cells from non-tumor cells in the biological sample to enrich the sample for tumor cells. In some embodiments, the agent is an EpCAM-conjugated magnetic beads. In some embodiments, the agent is an EpCAM-conjugated non-magnetic beads such as one used in flow-cytometry assays or immunohistochemistry assays.

[00256] In some embodiments, the kit further comprising reagents and instructions for: (i) attaching a detectable label to the tagged DNA fragments to produce labeled fragments; and (ii) contacting the detectable labeled fragments to the set of oligonucleotide probes.

[00257] In some embodiments, the kit further comprising instructions for determining a prognostic score indicative of the subject's responsiveness to one or more treatment modalities based on a differential score of the first epigenetic signature value and the second epigenetic value.

[00258] In some embodiments, the instruction comprises normalizing the differential value with at least one of a positive control value and a negative control value to obtain the prognostic score.

[00259] In some embodiments, the prognostic score is at least 0.6. In some embodiments, the prognostic score is less than 0.6.

[00260] In some embodiments, the kit further comprises reagents and instructions for detecting nuclear localization of a transcription factor selected from any one of transcription factors in Tables 2A and 2B.

[00261] In some embodiments, the transcription factors are selected from ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFH3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.

[00262] In some embodiments, the transcription factors are selected from at least 1, 2, 3, 4, 5, 6, 7, 8, 9, or 10 of transcription factors ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15,

GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFH3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.

[00263] In some embodiments, the transcription factors are selected ZKSCAN1A, HNF1B, or a combination thereof.

[00264] In some embodiments, the kit further comprises reagents and instructions for predicting a long duration of disease-free survival when the first epigenetic signature value is significantly lower than the second epigenetic signature value and/or predicting a short duration of disease-free survival when the first epigenetic signature value is significantly higher than the second epigenetic value.

[00265] In some embodiments, the kit further comprises reagents and instructions for determining a first phenotype and second phenotype of the subject's responsiveness to one or more treatment modalities.

[00266] In some embodiments, the first phenotype is recurrence of a cancer within 6 months, or 1, 2, 3, 4, or 5 years of surgical resection and/or the second phenotype is non-recurrence of a cancer within 6 months, or 1, 2, 3, 4, or 5 years of surgical resection. In some embodiments, the first phenotype is recurrence of a cancer within one year of surgical resection and the second phenotype is non-recurrence of a cancer within one year of surgical resection.

[00267] In some embodiments, the first phenotype is non-responder to a cancer therapy. In some embodiments, the second phenotype is responder to a cancer therapy. In some embodiments, the cancer therapy is selected from chemotherapy, immunotherapy, radiation, or combinations thereof.

[00268] In some embodiments, the second phenotype is having a median disease-free survival (DFS) of at least of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, or more years.

[00269] In some embodiments, the second phenotype is having a median disease-free survival (DFS) of at least 50, 100, 150, 200, 250, 300, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 1000, 1100, 1200, 1300, 1400, 1500, 1600, 1700, 1800, 1900, 2000, or more days.

[00270] In some embodiments, the second phenotype is having a median disease-free survival (DFS) of between 50 to 1500 days, between 100 to 1000 days, between 300 to 800 days, between 200 to 500 days, or between 400 to 600 days. In some embodiments, the first phenotype is having a median disease-free survival of at least 350 days.

[00271] In some embodiments, the first phenotype is having a median disease-free survival of less than 5, 4, 2, 3, 1 or less years. In some embodiments, the first phenotype is having a median disease-free survival of less than 12, 11, 10, 9, 8, 7, 6, 5, 4, 3, 2, 1 or less months. In some embodiments, the first phenotype is having a median disease-free survival of less than 350, 300, 250, 200, 150, 100, 50, 10, or less days. In some embodiments, the first phenotype is having a median disease-free survival of less than 50 days.

[00272] In some embodiments, the first phenotype is having a median disease-free survival of between 1 to 350 days, between 50-300 days, between 10-100 days, or between 40 to 250 days.

[00273] In some embodiments, the biological sample used to generate the ATAC-library, which can be used as ATAC-qPCR array template DNA, comprises treatment-naïve malignant cells obtained from a subject. In some embodiments, the subject is a treatment naïve patient who has not received the one or more treatment modalities.

[00274] In some embodiments, the subject is under treatment or has been treated with the one or more treatment modalities.

[00275] In some embodiments, the one or more treatment modalities are selected from resecting cancerous tissue, neo-adjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, an epigenetic drug, or combinations thereof. In some embodiments, the epigenetic drug is selected from DNMT inhibitor, an HDAC inhibitor, an EZH2 inhibitor, or combinations thereof. In some embodiments, the DNMT inhibitor is azacytidine or decitabine. In some embodiments, the HDAC inhibitor is vorinostat or romidepsin.

[00276] In some embodiments, the neo-adjuvant chemotherapy and/or adjuvant chemotherapy is selected from gemcitabine, nab-paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, leucovorin, capecitabine, cisplatin, or combinations thereof.

[00277] In some embodiments, the biological sample is selected from a tumor biopsy or surgically resected tumor specimen.

[00278] In some embodiments, obtaining the targeted accessible chromatin region fragments does not include sequencing the tagged fragments or amplicons thereof. In some embodiments, the amplified targeted accessible chromatin fragments comprise a mean size of about 50 bp to about 1100 bp, about 100 bp to about 350 bp, about 150bp to about 800 bp, about 80 bp to about 150 bp, or about 150 bp to about 400 bp. In some embodiments, the amplified targeted accessible chromatin fragments comprise a mean size of 80 bp, about 100 bp, about 120 bp, about 150 bp, about 180 bp, about 200 bp, about 250 bp, about 300 bp, about 400 bp, about 500 bp, about 600 bp, about 700 bp, about 800 bp, about 900 bp, about 1000 bp, about 1100 bp, or longer. In some embodiments, the amplified targeted accessible chromatin fragments comprise a mean size of about 120 bp.

8. EXAMPLES

8.1 EXAMPLE 1: PDAC Recurrence

[00279] A prospective cohort of treatment-naïve, surgically resected tumors from 54 PDAC patients was collected (n=54). PDAC malignant cells from freshly resected tumors were sorted using EpCAM-conjugated magnetic beads. Both EpCAM⁺ and EpCAM⁻ cells from each of the tumors were collected. The canonical variant allele frequencies (VAF) of pancreatic cancer driver genes *KRAS* and *TP53* in the EpCAM⁺ cells were both dramatically higher than that of the EpCAM⁻ cells ($P < 0.001$, t-test) confirming the effective enrichment of malignant epithelial cells in EpCAM⁺ subpopulation of the same tumor. This enrichment was further confirmed by transcriptome analysis, which demonstrated overexpression of epithelial genes in the EpCAM⁺ subpopulation, with corresponding expression of immune cell and collagen genes in the EpCAM⁻ subpopulation.

[00280] Assay for Transposase-Accessible Chromatin sequencing (ATAC-seq) was performed on the EpCAM⁺ cells to interrogate genome-wide chromatin accessibility and associated differentially accessible TF binding sites. A global atlas of 121,697 peaks with median width of 505bp, where each peak was reproducible in replicate ATAC-seq libraries for at least one patient was assembled. Saturation analysis was performed to estimate incremental new peak discovery associated with step-wise increases in sample size and confirmed that a sample size of n=40 approached saturating coverage.

[00281] Follow-up clinical data were available for 36 out of 40 patients included in the atlas. Nineteen (19) of 36 patients were at least 365 days post-treatment, among whom 9 patients (47.4%) had recurred (DFS $\leq$ 1 year, referred to as the recurrent group), and 10 patients had no recurrence (DFS

>1 year; maximum of 660 days, referred to as the non-recurrent group). The latter group, however, was expected to be mixture of long-term survivors and others who will recur in 2-5 years. For the discovery analyses, 3 patients who did not receive any adjuvant chemotherapy were excluded, leaving 16 patients (6 recurrent and 10 non-recurrent). A multi-factor generalized linear model was then used to identify significant differential chromatin accessibility events between the recurrent versus non-recurrent groups, while controlling for the effects of read depth and margin status.

[00282] More than one thousand (1092) open chromatin peaks were identified as being differentially accessible (absolute $\log_2$ fold change > 1 and FDR-adjusted $P < 0.001$) between the patients who recurred within a year of surgery and the patients who did not recur (maximum follow-up of 660 days) by ATAC-seq as in FIGs. 1A-1B. The differentially accessible chromatin regions are listed in Table 1.

Table 1.

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
17	52977819	52978913	promoter	ENST00000575909	TOMIL1	-1.01	2.2E-06	1094
10	134254015	134254324	promoter	ENST00000450206	RP11-432J24.3	1.56	9.0E-04	309
10	1506248	1507137	intron	ENST00000381312	ADARB2	1.30	5.1E-05	889
9	27625883	27626853	intergenic	ENST00000400348	CTAGE12P	-1.38	2.1E-08	970
14	105698636	105698888	intron	ENST00000550208	BRF1	1.35	1.6E-05	252
7	401254	401879	intergenic	ENST00000515213	AC226118.1	1.31	5.8E-04	625
7	4652611	4652868	intergenic	ENST00000446823	FO XK1	1.05	8.9E-04	257
22	23744503	23745176	promoter	ENST00000420968	ZDHHC8P1	-1.04	7.1E-04	673
X	3615234	3616144	intron	ENST00000262848	PRKX	-1.12	7.8E-04	910
17	104433	104716	intron	ENST00000570638	RPH3AL	1.45	9.4E-04	283
2	1420825	1421839	intron	ENST00000382198	TPO	1.08	8.6E-05	1014
16	12895395	12895819	promoter	ENST00000539677	CPPED1	1.20	1.6E-04	424
16	89495481	89495932	intron	ENST00000566973	ANKRD11	1.11	6.9E-04	451
16	1389753	1390364	intron	ENST00000421665	BAIAP3	1.24	3.3E-04	611
6	2504483	2504975	intergenic	ENST00000606884	GMDS-AS1	1.18	2.4E-04	492
2	2016399	2016710	intron	ENST00000479156	MYT1L	1.82	3.4E-08	311
17	75480980	75481368	intron	ENST00000585638	9-Sep	1.29	2.8E-04	388
22	30601850	30602161	promoter	ENST00000432360	RP3-438O4.4	1.44	6.3E-04	311
1	3594879	3595126	intron	ENST00000357733	TP73	1.36	1.2E-04	247

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
11	460271	461039	promoter	ENST00000526878	PTDSS2	1.32	1.2E-04	768
9	138020994	138021355	intergenic	ENST00000371796	OLFM1	1.35	2.4E-04	361
12	123933887	123934119	intergenic	ENST00000605712	RP11-972P1.8	1.34	2.2E-04	232
X	10087464	10087962	intron	ENST00000454666	WWC3	-1.50	7.4E-05	498
18	56179682	56180292	intron	ENST00000361673	ALPK2	1.07	2.5E-04	610
18	18970975	18971689	intron	ENST00000584611	RP11-296E23.1	-1.05	2.6E-04	714
17	106478	107040	intron	ENST00000570638	RPH3AL	1.30	1.9E-04	562
18	20512914	20514073	promoter	ENST00000578831	RP11-739L10.1	-1.03	3.8E-04	1159
11	70454	70919	intergenic	ENST00000519787	RP11-304M2.1	1.54	5.0E-04	465
2	242869770	242871341	intron	ENST00000429947	AC131097.3	1.15	3.2E-04	1571
19	40421670	40422156	intron	ENST00000221347	FCGBP	1.56	4.3E-04	486
11	92438452	92438798	intron	ENST00000525166	FAT3	1.03	5.5E-04	346
1	59246541	59247091	exon	ENST00000371222_43680		-1.40	4.0E-04	550
18	6413976	6415319	promoter	ENST00000580162	L3MBTL4	-1.20	3.9E-04	1343
14	67878683	67879198	promoter	ENST00000557388	PLEK2	-1.06	2.8E-05	515
10	51566723	51567262	promoter	ENST00000414907	NCOA4	-1.18	2.3E-04	539
11	128149728	128150176	intergenic	ENST00000608492	RP11-702B10.1	1.57	1.7E-04	448
20	5344571	5345402	intergenic	ENST00000363443	RNA5-8SP7	1.23	1.0E-04	831
10	106087848	106088405	promoter	ENST00000358187	ITPRIP	1.27	1.3E-05	557
20	17540069	17540372	promoter	ENST00000377868	BFSP1	1.24	2.4E-04	303
7	66017307	66017790	intron	ENST00000445080	GS1-124K5.12	1.08	1.2E-04	483
2	9445224	9446284	intron	ENST00000315273	ASAP2	1.04	9.6E-04	1060
4	84255872	84256464	promoter	ENST00000513463	HPSE	-1.06	8.7E-05	592
6	78359808	78360616	intergenic	ENST00000602452	MEI4	-1.49	2.7E-04	808
18	21017554	21018179	promoter	ENST00000399707	TMEM241	-1.15	3.3E-04	625
19	4084177	4084702	intergenic	ENST00000262948	MAP2K2	1.05	2.6E-04	525
7	36555230	36555979	promoter	ENST00000471806	AOAH	1.10	1.5E-04	749
3	18799504	18799922	intron	ENST00000425799	AC144521.1	-1.11	1.4E-10	418
8	86375420	86376638	promoter	ENST00000517697	RP11-317J10.2	-1.13	3.7E-09	1218
16	33345278	33346583	promoter	ENST00000568752	RP11-989E6.10	1.14	2.9E-04	1305
7	63220603	63221633	intergenic	ENST00000605464	CICP24	1.21	1.2E-04	1030
2	87651678	87651939	intergenic	ENST00000444323	AC068279.3	1.16	2.8E-04	261
22	19434714	19435523	promoter	ENST00000333059	C22orf39	-1.03	9.5E-04	809
3	126945866	126946636	intergenic	ENST00000492080	RP11-305F5.2	1.05	4.0E-04	770
11	2011127	2011556	promoter	ENST00000419080	MRPL23-AS1	1.54	1.0E-05	429

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
11	119612823	119613563	intergenic	ENST00000533253	CTD-2523D13.2	1.14	2.5E-04	740
1	1293633	1294442	promoter	ENST00000445648	MXRA8	1.33	1.9E-08	809
11	102364324	102364756	intron	ENST00000529278	RP11-315O6.2	-1.07	2.8E-05	432
1	117900726	117901380	intergenic	ENST00000604156	RP11-188D8.1	1.38	1.1E-04	654
7	102091876	102092500	exon	ENST00000356387_249477		1.38	3.5E-04	624
10	92690759	92691502	intergenic	ENST00000364734	RNU6-740P	1.09	6.7E-04	743
10	135342280	135342918	promoter	ENST00000599428	AL161645.2	1.69	7.1E-06	638
12	124857925	124858331	intron	ENST00000448614	NCOR2	1.14	4.6E-04	406
18	9474785	9475995	promoter	ENST00000383432	RALBP1	-1.03	3.7E-04	1210
X	20396229	20397054	intergenic	ENST00000517169	RN7SKP183	-1.25	4.1E-04	825
1	2111576	2112325	intron	ENST00000505322	PRKCZ	1.32	4.8E-04	749
4	71450043	71450658	intergenic	ENST00000322937	AMBN	-1.15	9.9E-05	615
11	1086528	1086937	intron	ENST00000359061	MUC2	1.19	7.0E-05	409
2	10539305	10539660	intron	ENST00000419810	HPCAL1	1.24	6.7E-05	355
16	33348985	33350971	promoter	ENST00000568752	RP11-989E6.10	1.18	4.8E-05	1986
21	47410321	47410540	intron	ENST00000361866	COL6A1	1.19	3.5E-04	219
19	36774890	36775141	intergenic	ENST00000586345	CTD-3162L10.1	1.18	9.4E-04	251
19	36790418	36790944	intergenic	ENST00000586345	CTD-3162L10.1	1.40	1.8E-05	526
19	36791007	36791167	intergenic	ENST00000586345	CTD-3162L10.1	1.61	2.0E-04	160
16	32297453	32298796	intergenic	ENST00000568567	RP11-17M15.2	1.16	3.0E-05	1343
19	36785355	36785870	intergenic	ENST00000586345	CTD-3162L10.1	1.28	7.8E-04	515
12	9558298	9559027	intron	ENST00000540982	RP11-599J14.2	1.17	4.1E-04	729
3	125726687	125727535	promoter	ENST00000504118	SLC41A3	1.08	6.4E-04	848
10	129058797	129060504	intron	ENST00000464466	DOCK1	1.09	3.6E-04	1707
2	87642804	87643025	intergenic	ENST00000444323	AC068279.3	1.10	3.8E-04	221
1	11296642	11297523	intron	ENST00000361445	MTOR	1.43	9.5E-04	881
12	31871662	31871945	intron	ENST00000509386	AMN1	1.78	8.9E-05	283
5	1521927	1522688	promoter	ENST00000514484	LPCAT1	1.23	2.7E-06	761
1	4692485	4692949	intergenic	ENST00000378190	AJAP1	1.15	9.3E-04	464
1	66655817	66656717	intron	ENST00000412480	PDE4B	1.25	5.2E-04	900
1	16970486	16970660	promoter	ENST00000362058	CROCCP2	1.01	7.5E-05	174
19	6677696	6678735	promoter	ENST00000601475	C3	1.13	5.3E-04	1039
1	56933904	56934476	intergenic	ENST00000371250	PPAP2B	1.32	2.7E-04	572
1	4693158	4693721	intergenic	ENST00000378190	AJAP1	1.10	2.8E-04	563
12	123333197	123333659	promoter	ENST00000536772	HIP1R	1.13	9.0E-04	462

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
1	193406539	193407729	intergenic	ENST00000420807	LINC01031	1.07	5.6E-04	1190
3	121723306	121724477	promoter	ENST00000462014	ILDR1	1.05	9.6E-04	1171
2	209676292	209676942	intron	ENST00000419079	PTH2R	1.38	3.6E-04	650
12	3306839	3307985	intron	ENST00000011898	TSPAN9	1.42	5.2E-04	1146
11	94615832	94616486	intron	ENST00000545958	RP11-856F16.2	1.10	6.5E-04	654
1	3604957	3605264	promoter	ENST00000378280	TP73	1.32	3.3E-04	307
2	1391878	1392649	intron	ENST00000497517	TPO	1.05	5.7E-04	771
1	811189	812119	promoter	ENST00000427857	FAM41C	1.07	4.0E-04	930
19	38468627	38469128	intron	ENST00000476317	SIPA1L3	1.28	8.3E-04	501
1	238292984	238293512	intergenic	ENST00000445891	YWHAQP9	1.34	6.1E-05	528
13	39210941	39211343	intergenic	ENST00000447765	PRDX3P3	-1.33	4.0E-04	402
5	42811882	42812507	promoter	ENST00000508937	SEPP1	-1.05	1.9E-05	625
2	1560598	1560978	intron	ENST00000438247	AC144450.1	1.15	1.5E-04	380
12	132815639	132815889	intron	ENST00000328957	GALNT9	1.20	9.9E-04	250
9	115846414	115847424	intergenic	ENST00000439875	FAM225B	1.27	1.8E-04	1010
19	54613041	54613311	promoter	ENST00000482960	NDUFA3	1.72	2.1E-06	270
2	239204444	239205433	intergenic	ENST00000437372	AC012485.2	1.28	1.9E-04	989
11	397903	398909	promoter	ENST00000526971	PKP3	1.04	2.5E-04	1006
1	1912821	1913709	intron	ENST00000468610	C1orf222	1.43	3.6E-06	888
19	37782096	37782418	intergenic	ENST00000586442	CTD-3220F14.1	1.63	6.4E-04	322
2	11776847	11777488	intron	ENST00000396123	GREB1	1.34	6.0E-05	641
12	132813440	132813985	intron	ENST00000328957	GALNT9	1.07	6.4E-04	545
1	110663023	110663256	intergenic	ENST00000334179	UBL4B	1.20	8.9E-04	233
7	155893958	155894405	intergenic	ENST00000384333	Y_RNA	1.04	4.3E-04	447
20	36202030	36202951	intergenic	ENST00000423261	GLRXP	1.04	5.1E-04	921
1	228778123	228778480	promoter	ENST00000365055	RNA5S15	1.08	1.6E-05	357
1	4503130	4503709	intergenic	ENST00000423197	RP5-1166F10.1	1.15	8.4E-04	579
20	62781169	62781776	promoter	ENST00000360149	MYT1	1.23	6.1E-04	607
18	8890911	8891510	intergenic	ENST00000359865	SOGA2	-1.21	4.2E-04	599
14	64330729	64331355	promoter	ENST00000556725	SYNE2	-1.09	1.1E-06	626
3	195509793	195510202	exon	ENST00000478156_152007		1.45	8.0E-05	409
11	134831292	134832253	intergenic	ENST00000528497	RP11-555G19.1	1.30	3.1E-04	961
5	11443246	11443549	intron	ENST00000508761	CTNND2	1.41	3.7E-04	303
9	140244387	140245281	intron	ENST00000484392	EXD3	1.09	6.4E-04	894
19	39648485	39649257	promoter	ENST00000599657	PAK4	1.37	6.4E-04	772

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
10	132271970	132272400	intron	ENST00000439421	RP11-540N6.1	1.08	5.1E-04	430
11	41553950	41554439	intron	ENST00000526978	RP11-124G5.3	1.17	9.1E-04	489
1	247292118	247293363	intron	ENST00000476312	ZNF124	1.35	3.0E-06	1245
20	61588799	61589615	intron	ENST00000411611	SLC17A9	1.10	7.6E-04	816
19	30056819	30058660	intergenic	ENST00000335523	VSTM2B	1.09	5.4E-04	1841
19	49337650	49338689	promoter	ENST00000595764	HSD17B14	1.14	4.5E-04	1039
1	37259254	37259535	intergenic	ENST00000373091	GRIK3	1.12	9.6E-04	281
12	131780776	131781831	promoter	ENST00000508505	RP11-495K9.3	1.00	9.5E-04	1055
19	32223716	32224929	intergenic	ENST00000365024	RNU6-967P	1.19	4.6E-04	1213
2	211054239	211055494	intron	ENST00000412065	AC006994.2	-1.02	8.6E-04	1255
1	37449602	37450029	intron	ENST00000373093	GRIK3	1.00	9.5E-04	427
1	40128961	40129465	intron	ENST00000235628	NT5C1A	1.12	2.4E-04	504
14	38677991	38678610	promoter	ENST00000267377	SSTR1	-1.26	6.9E-04	619
1	4769995	4770757	promoter	ENST00000466761	AJAPI	1.13	4.4E-04	762
21	47318748	47319014	promoter	ENST00000468429	PCBP3	1.07	5.3E-04	266
19	34280154	34280686	intergenic	ENST00000587658	KCTD15	1.16	3.4E-04	532
X	23522303	23522698	intergenic	ENST00000458766	snoU13	-1.03	9.0E-04	395
13	108686039	108687002	intergenic	ENST00000375915	FAM155A	-1.67	1.9E-10	963
21	16512741	16513203	intergenic	ENST00000449746	AF127577.12	-1.46	1.2E-05	462
4	69817171	69817631	promoter	ENST00000251566	UGT2A3	-1.81	3.2E-07	460
1	224136990	224138052	promoter	ENST00000424045	CICP5	1.03	3.7E-04	1062
11	1796937	1797410	intergenic	ENST00000449749	AC068580.7	1.36	3.0E-04	473
11	132947949	132948284	intron	ENST00000529038	OPCML	1.09	6.7E-04	335
1	1276059	1277202	intron	ENST00000472445	DVL1	1.09	6.2E-04	1143
X	2526973	2527761	promoter	ENST00000527459	CD99P1	-1.15	1.8E-04	788
14	72448205	72449425	intron	ENST00000402788	RGS6	1.05	1.9E-04	1220
18	21718709	21719338	promoter	ENST00000327201	CABYR	-1.41	1.3E-05	629
18	21851298	21852369	promoter	ENST00000585247	OSBPL1A	-1.02	9.0E-05	1071
4	170121436	170122132	promoter	ENST00000510225	RP11-327O17.2	-1.07	2.8E-04	696
14	77589823	77590311	intron	ENST00000557752	RP11-463C8.4	-1.04	2.7E-04	488
3	65938946	65939447	promoter	ENST00000460754	MAGI1-IT1	-1.18	1.7E-04	501
12	10826411	10827032	promoter	ENST00000541561	STYK1	-1.10	3.7E-04	621
13	76334271	76334966	promoter	ENST00000465261	LMO7	-1.05	1.4E-04	695
4	106816201	106816854	promoter	ENST00000503451	NPNT	-1.33	3.6E-07	653
8	119890394	119891274	intergenic	ENST00000297350	TNFRSF11B	-1.32	3.8E-05	880

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
18	3230353	3230820	intron	ENST00000580139	RP13-270P17.2	-1.94	8.6E-05	467
4	23789895	23790557	intron	ENST00000509702	PPARGC1A	-1.28	2.2E-05	662
4	72978120	72978772	intron	ENST00000358749	NPFFR2	-1.41	3.0E-10	652
6	53719637	53720021	intron	ENST00000370882	LRRC1	-1.16	1.3E-04	384
18	59561256	59561922	promoter	ENST00000588396	RNF152	-1.14	5.4E-05	666
5	158122586	158122909	intergenic	ENST00000519890	EBF1	-1.36	6.3E-04	323
6	43894454	43895332	intergenic	ENST00000422059	RP5-1120P11.1	-1.20	7.8E-06	878
17	38439964	38440892	intron	ENST00000323571	WIPF2	-1.26	1.2E-04	928
4	103541806	103542546	intergenic	ENST00000226574	NFKB1	-1.01	1.9E-07	740
5	170176920	170177427	intron	ENST00000521965	MIR4454	-1.15	1.7E-04	507
4	25864064	25865011	promoter	ENST00000513364	SEL1L3	-1.12	1.5E-04	947
12	15815552	15815954	promoter	ENST00000540613	EPS8	-1.00	7.9E-05	402
19	11545786	11546623	promoter	ENST00000586836	CCDC151	-1.05	9.7E-05	837
X	13006739	13007333	intergenic	ENST00000451311	TMSB4X	-1.36	1.0E-05	594
18	21692827	21693592	promoter	ENST00000540918	TTC39C	-1.64	1.9E-06	765
9	27371349	27371791	intron	ENST00000603061	MOB3B	-1.44	3.6E-09	442
18	29738048	29738594	intron	ENST00000583696	GAREM	-1.59	4.8E-04	546
3	18699491	18700274	intron	ENST00000595388	AC144521.1	-1.65	5.8E-06	783
7	158995654	158996480	intergenic	ENST00000437005	PIP5K1P2	1.08	5.5E-04	826
12	15865506	15866240	promoter	ENST00000543612	EPS8	-1.41	7.0E-07	734
4	155547868	155548555	promoter	ENST00000499392	LRAT	-1.02	6.5E-04	687
5	106810443	106811097	intron	ENST00000505499	EFNA5	-1.08	3.5E-04	654
17	39956851	39957456	intergenic	ENST00000355468	LEPREL4	-1.11	8.9E-04	605
18	68048808	68049145	exon	ENST00000582251_572674		-1.16	1.3E-05	337
20	22471368	22471859	intergenic	ENST00000420070	LINC00261	-1.14	8.0E-04	491
13	61989175	61989676	promoter	ENST00000409204	PCDH20	-1.39	1.7E-05	501
5	78791005	78791692	intron	ENST00000535690	HOMER1	-1.57	1.1E-08	687
1	157210261	157210939	intergenic	ENST00000449345	RP11-85G21.1	-1.09	5.7E-04	678
17	56591826	56592157	promoter	ENST00000582390	MTMR4	-1.12	3.1E-04	331
1	27240311	27240999	promoter	ENST00000254227	NR0B2	-1.34	2.6E-04	688
4	149366324	149366956	promoter	ENST00000344721	NR3C2	-1.25	2.5E-05	632
13	74861868	74862243	promoter	ENST00000383890	RNY1P5	-1.51	9.2E-07	375
15	53745621	53746295	intergenic	ENST00000567224	WDR72	-1.62	2.4E-08	674
7	87198356	87198910	intron	ENST00000543898	ABCB1	-1.22	3.7E-05	554
4	38134715	38135185	promoter	ENST00000492180	TBC1D1	-1.18	4.6E-05	470

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
18	77005558	77006476	intron	ENST00000587878	ATP9B	1.10	2.1E-04	918
4	42658842	42659808	promoter	ENST00000562054	RP11-109E24.2	-1.11	1.3E-05	966
8	128309764	128310584	intron	ENST00000523825	CASC8	-1.23	2.4E-04	820
18	25236246	25236678	intergenic	ENST00000584546	RP11-739N10.1	-1.75	1.7E-04	432
4	83316004	83316436	intergenic	ENST00000503202	IGBP4	-1.15	3.0E-05	432
18	3773069	3773731	promoter	ENST00000584060	RP11-874J12.3	-2.08	3.4E-08	662
1	65210283	65210996	promoter	ENST00000371072	RAVER2	-1.16	7.6E-05	713
4	22970924	22971638	intergenic	ENST00000511453	RP11-412P11.1	-1.27	2.9E-07	714
15	29966880	29967293	promoter	ENST00000536835	RP11-680F8.1	-1.31	5.6E-05	413
8	4195706	4196553	intron	ENST00000539096	CSMD1	-2.07	1.4E-09	847
18	21594009	21595594	promoter	ENST00000579713	RP11-403A21.2	-1.10	8.6E-05	1585
18	13823915	13824237	promoter	ENST00000390194	AP001525.1	-1.11	8.9E-05	322
17	48845654	48846094	promoter	ENST00000502517	LINC00483	-1.26	3.3E-04	440
8	22601135	22601604	promoter	ENST00000519624	RP11-459E5.1	-1.06	1.5E-04	469
X	19352288	19352590	intergenic	ENST00000379806	PDHA1	-1.30	5.2E-04	302
14	65346358	65347344	promoter	ENST00000542895	SPTB	-1.01	2.5E-04	986
15	64540179	64540503	intron	ENST00000606793	CTD-2116N17.1	-1.00	3.2E-04	324
6	82547755	82548150	intergenic	ENST00000418567	RP11-379B8.1	-1.18	2.1E-05	395
11	104322692	104323628	intron	ENST00000536529	RP11-886D15.1	-1.28	9.9E-05	936
17	46342828	46343603	intron	ENST00000581419	SKAP1	-1.10	2.3E-04	775
2	146971789	146972404	intergenic	ENST00000413391	RPL17P12	-1.68	2.1E-08	615
X	24517071	24517405	intron	ENST00000493226	PDK3	-1.04	8.8E-04	334
12	15323979	15324554	intron	ENST00000393736	RERG	-2.21	7.2E-14	575
14	73928913	73929398	promoter	ENST00000561382	RP1-240K6.3	-1.13	4.9E-07	485
12	71556548	71557645	intron	ENST00000549421	TSPAN8	-1.66	4.2E-05	1097
4	77625261	77626040	intron	ENST00000486758	SHROOM3	-1.47	1.7E-09	779
14	53167381	53167871	intergenic	ENST00000556039	ERO1L	-1.06	1.8E-04	490
15	83349039	83349480	promoter	ENST00000543938	AP3B2	-1.68	4.4E-05	441
18	28591355	28591777	intron	ENST00000434452	DSC3	-1.70	3.6E-04	422
6	30226869	30227564	promoter	ENST00000420110	HLA-L	-1.04	4.9E-07	695
12	12550932	12551724	intron	ENST00000298571	LOH12CR1	-1.06	7.7E-04	792
18	7926531	7927006	intron	ENST00000400053	PTPRM	-1.56	9.3E-07	475
5	156874176	156874688	intron	ENST00000519499	CTB-109A12.1	-1.29	6.0E-05	512
4	105415971	105416679	promoter	ENST00000466963	CXXC4	-1.12	2.8E-07	708
1	247526375	247526698	intergenic	ENST00000478225	ZNF496	1.35	3.8E-04	323

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
14	68205454	68206247	intron	ENST00000394455	ZFYVE26	-1.09	1.8E-05	793
18	21977090	21978175	promoter	ENST00000582618	OSBPL1A	-1.13	5.8E-04	1085
5	31020930	31021844	intergenic	ENST00000495944	RPL19P11	-1.60	3.8E-06	914
17	73597354	73597809	promoter	ENST00000584323	MYO15B	-1.01	3.9E-04	455
1	165614855	165615573	promoter	ENST00000461759	MGST3	-1.15	2.6E-04	718
12	89466458	89467244	intron	ENST00000549278	RP11-13A1.3	-1.99	6.4E-04	786
4	139120636	139121025	intron	ENST00000509248	SLC7A11	-1.06	2.2E-04	389
8	103941579	103942473	promoter	ENST00000517996	KB-1507C5.2	-1.07	8.4E-09	894
15	36469921	36470501	intron	ENST00000561394	RP11-184D12.1	-1.53	9.4E-04	580
8	15397612	15398367	promoter	ENST00000503731	TUSC3	-1.80	5.8E-05	755
7	98013278	98014497	promoter	ENST00000398259	RPS3AP26	-1.20	2.7E-04	1219
18	3051740	3052729	intergenic	ENST00000356443	MYOM1	-1.45	3.8E-05	989
15	98491142	98491429	intron	ENST00000538249	ARRDC4	-1.05	4.7E-04	287
X	24167349	24168808	promoter	ENST00000427551	ZFX-AS1	-1.12	9.2E-07	1459
13	30682897	30683442	promoter	ENST00000432770	LINC00365	-1.02	6.8E-04	545
10	65479858	65480099	intron	ENST00000444770	RP11-170M17.1	-1.28	2.0E-06	241
22	43336262	43336736	intron	ENST00000453079	PACSIN2	-1.07	4.8E-04	474
18	24235854	24237453	promoter	ENST00000584630	KCTD1	-1.21	1.1E-04	1599
18	29665002	29665389	intron	ENST00000583184	RP11-53I6.2	-1.47	4.1E-04	387
X	123540218	123540808	intron	ENST00000469481	STAG2	-1.15	2.0E-06	590
21	29628568	29629059	intergenic	ENST00000453420	AL035610.2	-1.35	1.8E-05	491
14	24777038	24777597	promoter	ENST00000554411	CIDEB	-1.09	5.1E-06	559
7	90350197	90350681	intron	ENST00000436577	CDK14	-1.28	5.1E-05	484
3	118930104	118930466	intergenic	ENST00000483209	B4GALT4	-1.33	9.1E-04	362
17	33759489	33760107	promoter	ENST00000304905	SLFN12	-1.36	3.0E-05	618
6	126265396	126265975	intergenic	ENST00000229633	HINT3	-1.22	5.2E-05	579
18	8341512	8342175	intron	ENST00000577827	PTPRM	-1.38	7.6E-05	663
13	60586478	60586983	promoter	ENST00000435636	DIAPH3-AS1	-1.16	2.0E-04	505
2	43232429	43233212	promoter	ENST00000457457	AC016735.1	-1.36	2.3E-07	783
4	72052163	72052582	promoter	ENST00000264485	SLC4A4	-1.53	1.8E-07	419
18	11005554	11005954	intron	ENST00000582913	PIEZO2	-1.21	3.1E-05	400
6	52254401	52254862	intron	ENST00000360726	PAQR8	-1.13	1.8E-05	461
16	1031471	1032054	promoter	ENST00000565467	RP11-161M6.2	-1.39	3.3E-04	583
14	68987627	68988132	intron	ENST00000478014	RAD51B	-1.03	2.2E-06	505
4	38387157	38387752	intron	ENST00000503465	RP11-83C7.1	-1.45	1.6E-12	595

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Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
12	18951259	18952375	intergenic	ENST00000317658	CAPZA3	-1.17	8.8E-04	1116
8	74219833	74220352	intron	ENST00000520894	RP11-434I12.2	-1.28	8.7E-04	519
11	134526444	134526989	intergenic	ENST00000529417	RP11-469N6.3	2.13	6.3E-08	545
10	108273148	108273531	intergenic	ENST00000399415	RP11-446H13.2	-1.96	1.5E-04	383
2	165770474	165770888	promoter	ENST00000483641	SLC38A11	-1.19	5.7E-05	414
9	28915264	28915864	intergenic	ENST00000401120	MIR873	-1.80	1.7E-04	600
1	244231070	244231550	intron	ENST00000598000	AL590483.1	-1.21	4.3E-04	480
4	24384043	24384371	intergenic	ENST00000410330	AC092846.1	-1.10	5.1E-05	328
5	103398196	103398978	intergenic	ENST00000514769	RP11-138J23.1	-1.19	9.4E-04	782
8	1878704	1879351	intron	ENST00000522435	ARHGEF10	-1.31	3.5E-04	647
8	37159582	37160492	intergenic	ENST00000518765	RP11-527N22.1	-1.01	2.5E-04	910
19	10859669	10860777	intron	ENST00000586939	DNM2	-1.13	1.9E-04	1108
8	38124767	38125231	promoter	ENST00000530193	PPAPDC1B	-1.13	8.4E-05	464
14	100625737	100626234	promoter	ENST00000553834	DEGS2	-1.04	8.6E-04	497
17	70514867	70515633	intron	ENST00000580861	LINC00511	-1.10	1.8E-04	766
11	22213851	22215484	promoter	ENST00000324559	ANO5	-1.10	5.0E-06	1633
11	91530137	91530591	promoter	ENST00000581290	RP11-201M22.1	-1.11	8.9E-04	454
4	174112844	174113342	intron	ENST00000512285	GALNT7	-1.32	1.1E-04	498
8	98861557	98862712	intron	ENST00000521545	LAPTM4B	-1.07	3.5E-04	1155
12	132401688	132401954	promoter	ENST00000540647	ULK1	1.88	3.5E-05	266
10	98623698	98624364	intron	ENST00000371097	LCOR	-1.04	8.8E-04	666
5	67497853	67498258	intergenic	ENST00000520762	RP11-404L6.2	-1.34	1.8E-04	405
8	71115117	71115743	intron	ENST00000518287	NCOA2	-1.46	1.6E-05	626
18	20695658	20696122	intergenic	ENST00000400473	CABLES1	-1.22	4.5E-05	464
18	19577616	19577921	promoter	ENST00000577673	AC091043.1	-1.35	1.3E-05	305
17	72746567	72746861	promoter	ENST00000585285	MIR3615	-1.28	8.9E-05	294
18	19866602	19866925	intergenic	ENST00000459476	snoU13	-1.38	3.8E-06	323
1	2688905	2690000	intron	ENST00000401095	TTC34	1.02	3.3E-04	1095
12	15842656	15843267	intron	ENST00000544064	EPS8	-1.26	9.2E-07	611
5	54467950	54468191	promoter	ENST00000516047	MIR449C	-1.04	4.2E-06	241
12	19219371	19219904	intergenic	ENST00000449390	RPL7P6	-1.53	1.4E-04	533
2	109002050	109002496	intron	ENST00000409309	SULT1C4	-1.20	5.7E-04	446
4	40475810	40476436	promoter	ENST00000507180	RBM47	-1.30	1.1E-05	626
4	115484596	115485293	intergenic	ENST00000310836	UGT8	-1.13	1.7E-04	697
5	56731545	56732157	intron	ENST00000506106	CTD-2023N9.1	-1.02	1.9E-04	612

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
5	98215879	98216617	intron	ENST00000284049	CHD1	-1.03	8.2E-04	738
6	155649620	155650370	intergenic	ENST00000475849	TFB1M	-1.27	4.6E-04	750
8	23039576	23039972	intergenic	ENST00000518308	RP11-1149O23.2	-1.07	8.2E-04	396
14	65409340	65409856	promoter	ENST00000557323	GPX2	-1.13	1.8E-05	516
18	12659958	12660445	promoter	ENST00000589405	PSMG2	-1.99	1.3E-06	487
16	57286027	57286608	promoter	ENST00000564376	RP11-407G23.3	-1.45	1.3E-04	581
12	89900906	89901589	intron	ENST00000546830	POC1B	-1.67	2.2E-05	683
3	172635673	172636396	intron	ENST00000351008	SPATA16	-1.28	3.0E-04	723
6	56263991	56264896	intergenic	ENST00000370819	COL21A1	-1.30	2.7E-05	905
8	86459177	86459730	intergenic	ENST00000520459	RP11-317J10.4	-1.05	8.6E-04	553
18	21699037	21699241	promoter	ENST00000583782	RP11-799B12.2	-1.68	9.4E-07	204
8	4188712	4189987	intron	ENST00000539096	CSMD1	-1.19	7.6E-05	1275
15	41324040	41324393	intron	ENST00000558357	INO80	3.06	1.2E-04	353
7	57265415	57265595	promoter	ENST00000423752	RP11-1217F2.13	2.76	6.9E-04	180
12	7055207	7055997	promoter	ENST00000538318	PTPN6	-1.13	4.7E-05	790
1	73361638	73361801	intron	ENST00000445976	RP4-660H19.1	2.75	4.5E-04	163
2	15499821	15500945	intron	ENST00000442506	NBAS	2.05	8.1E-04	1124
6	97944099	97944304	intergenic	ENST00000574739	RP3-418C23.2	2.08	1.3E-04	205
19	31869090	31869843	intron	ENST00000585336	AC007796.1	1.50	9.7E-04	753
17	80544014	80544489	promoter	ENST00000575578	FOXK2	1.24	2.5E-04	475
7	148469337	148470194	intron	ENST00000325222	CUL1	1.23	9.7E-04	857
10	129595626	129595975	intergenic	ENST00000388920	FOXI2	1.21	7.1E-04	349
2	217237783	217238658	promoter	ENST00000273067	4-Mar	1.66	2.3E-04	875
19	38489929	38490545	intron	ENST00000476317	SIPA1L3	2.18	4.3E-06	616
10	133797280	133797729	promoter	ENST00000368636	BNIP3	1.38	2.4E-04	449
10	133661124	133661318	intergenic	ENST00000341866	AL450307.1	1.96	9.7E-04	194
2	36129295	36129643	intergenic	ENST00000431951	MRPL50P1	1.77	6.1E-04	348
4	122791099	122792004	promoter	ENST00000567769	RP11-63B13.1	-1.05	3.2E-04	905
10	96989136	96989837	promoter	ENST00000451737	RP11-310E22.4	1.48	3.7E-04	701
12	6387233	6388200	intergenic	ENST00000539998	RP1-96H9.5	-1.01	1.6E-04	967
1	237963084	237963484	promoter	ENST00000466626	RYS2	-1.15	6.8E-04	400
11	117109912	117110426	exon	ENST00000529869_361297		1.45	8.5E-04	514
9	137494257	137495098	intergenic	ENST00000371817	COL5A1	1.68	1.7E-04	841
19	35809800	35810562	promoter	ENST00000601414	CD22	1.10	1.0E-04	762
19	38530496	38531253	intron	ENST00000476317	SIPA1L3	2.28	9.2E-07	757

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
12	108876411	108877044	intron	ENST00000502160	RP11-13G14.4	1.73	3.5E-05	633
1	210612139	210613054	promoter	ENST00000367009	HHAT	1.58	2.2E-04	915
7	157599753	157600564	intron	ENST00000404321	PTPRN2	1.35	2.6E-04	811
17	68185179	68185450	intergenic	ENST00000243457	KCNJ2	1.93	3.5E-04	271
19	30019124	30019835	promoter	ENST00000579268	CTC-525D6.2	1.50	6.3E-04	711
7	154861699	154862044	promoter	ENST00000287907	HTR5A	1.23	1.5E-04	345
7	2915618	2916223	intergenic	ENST00000396946	CARD11	1.24	8.6E-04	605
3	168602522	168603249	intergenic	ENST00000484765	RP11-368I23.2	1.30	6.4E-04	727
2	15309734	15310359	intron	ENST00000485694	NBAS	1.55	1.8E-04	625
19	33367595	33368355	promoter	ENST00000586628	CTD-2085J24.4	1.70	7.0E-05	760
11	117151727	117152451	promoter	ENST00000524917	RNF214	1.29	6.4E-04	724
12	116400382	116401203	promoter	ENST00000549725	RP11-493P1.2	1.69	2.6E-05	821
4	85420209	85421036	promoter	ENST00000295886	NKX6-1	-1.14	1.9E-04	827
19	37793700	37794465	intergenic	ENST00000591471	HKR1	1.62	3.6E-04	765
3	183894085	183894896	promoter	ENST00000431779	AP2M1	1.02	2.5E-04	811
16	86985326	86986094	intergenic	ENST00000566109	RP11-107C10.1	1.33	4.8E-04	768
3	14203211	14203401	intron	ENST00000477324	XPC	2.20	3.0E-04	190
16	28394898	28395627	intron	ENST00000398943	EIF3CL	1.66	3.5E-04	729
19	42617722	42618169	intron	ENST00000531773	POU2F2	1.24	8.3E-04	447
1	165868016	165868540	promoter	ENST00000463772	UCK2	1.08	8.5E-04	524
5	79715065	79715253	intron	ENST00000510995	ZFYVE16	2.32	2.0E-04	188
X	44731642	44733410	promoter	ENST00000475233	KDM6A	-1.02	7.2E-05	1768
19	36095937	36096410	intergenic	ENST00000589603	AC002115.9	1.37	9.3E-05	473
16	28742292	28743038	promoter	ENST00000569005	EIF3C	1.36	6.4E-04	746
18	21032725	21033693	promoter	ENST00000577501	RIOK3	-1.05	5.2E-04	968
11	12185010	12186343	promoter	ENST00000379612	MICAL2	1.03	9.2E-04	1333
14	76815171	76815651	promoter	ENST00000390772	AC016543.1	1.20	6.3E-04	480
17	21305235	21305901	intron	ENST00000583088	KCNJ12	1.03	7.6E-04	666
9	137394472	137395015	intergenic	ENST00000444936	RP11-473E2.2	1.21	7.7E-04	543
19	38704515	38705167	promoter	ENST00000488378	DPF1	1.71	5.1E-06	652
8	143273979	143275177	intergenic	ENST00000517704	LINC00051	1.44	3.1E-05	1198
18	24060728	24061749	intron	ENST00000578973	KCTD1	-1.30	2.7E-04	1021
11	20118774	20119500	intron	ENST00000311043	NAV2	1.49	6.7E-04	726
14	56298766	56299226	intergenic	ENST00000560336	LINC00520	-1.01	6.7E-05	460
20	22392204	22392708	intron	ENST00000377121	RP5-1004I9.1	-1.09	5.9E-04	504

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
19	39564251	39564693	intergenic	ENST000000601575	PAPL	1.36	8.2E-05	442
3	126326051	126326334	promoter	ENST00000519162	TXNRD3	1.54	5.5E-04	283
5	89316952	89317321	intergenic	ENST00000584845	MIR3660	-1.03	4.1E-04	369
11	117069701	117070445	promoter	ENST00000278968	TAGLN	1.19	4.0E-04	744
1	19586986	19587534	intergenic	ENST00000330263	MRT04	1.32	5.2E-04	548
15	26020460	26021175	intron	ENST00000555815	ATP10A	1.33	1.3E-06	715
2	102353912	102354557	intron	ENST00000417294	MAP4K4	-1.29	7.3E-05	645
4	141264454	141264871	promoter	ENST00000506322	SCOC	-1.08	3.8E-05	417
2	242054831	242055272	intron	ENST00000493544	PASK	1.77	1.7E-06	441
17	39686341	39686778	promoter	ENST00000361566	KRT19	-1.12	1.3E-04	437
13	42270599	42271143	promoter	ENST00000478987	VWA8	-1.26	3.1E-04	544
19	33236950	33238144	intron	ENST00000421545	TDRD12	1.04	4.6E-04	1194
12	33049306	33050344	promoter	ENST00000546741	PKP2	-1.04	1.4E-04	1038
10	81239097	81239352	intergenic	ENST00000557620	TPRX1P1	1.62	4.5E-04	255
20	36919560	36920024	exon	ENST00000451435_619426		1.18	1.8E-04	464
10	126028465	126028958	intergenic	ENST00000539214	OAT	1.54	9.5E-04	493
11	120088623	120089064	intron	ENST00000531220	OAF	1.43	7.0E-04	441
15	51369174	51369713	intron	ENST00000559909	RP11-108K3.1	1.16	4.6E-04	539
16	19843028	19843331	intron	ENST00000568061	IQCK	1.29	9.5E-04	303
X	1510891	1512012	promoter	ENST00000484026	SLC25A6	-1.04	8.6E-04	1121
3	71591682	71592117	promoter	ENST00000408337	MIR1284	1.17	1.5E-04	435
19	33963942	33964303	intron	ENST00000590408	PEPD	1.31	3.3E-04	361
17	64536177	64536808	intron	ENST00000284384	PRKCA	1.39	9.4E-04	631
11	1078428	1079839	intron	ENST00000359061	MUC2	1.34	8.4E-04	1411
12	98793216	98793758	intergenic	ENST00000364426	RNU4-41P	1.16	2.4E-05	542
1	15322511	15323031	intron	ENST00000400797	KAZN	1.15	4.6E-04	520
2	208352490	208352976	intron	ENST00000418850	AC007879.5	1.98	2.9E-04	486
3	128914473	128915151	intergenic	ENST00000422453	CNBP	1.16	4.6E-04	678
6	110064994	110065287	intron	ENST00000230124	FIG4	1.24	5.5E-04	293
7	86688557	86689480	promoter	ENST00000423294	KIAA1324L	-1.09	2.5E-04	923
3	127453590	127454743	promoter	ENST00000398101	MGLL	1.22	1.0E-04	1153
9	127105090	127105743	intron	ENST00000539416	NEK6	1.31	1.7E-04	653
4	99064059	99065056	promoter	ENST00000295268	STPG2	-1.10	9.8E-07	997
11	70496478	70496740	intron	ENST00000445654	SHANK2	1.30	6.5E-06	262
11	1691687	1692395	intergenic	ENST00000382167	FAM99A	1.49	4.4E-05	708

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
4	173647115	173647791	intron	ENST00000508122	GALNTL6	-1.60	1.3E-05	676
14	102172379	102172956	intron	ENST00000557778	RP11-1029J19.5	1.02	4.1E-04	577
18	21082967	21083951	promoter	ENST00000592119	C18orf8	-1.12	9.3E-05	984
7	150810759	150811221	promoter	ENST00000335367	AGAP3	1.13	4.0E-04	462
2	74010590	74010935	promoter	ENST00000409561	C2orf78	1.10	3.0E-04	345
10	133759398	133760269	intron	ENST00000472664	PPP2R2D	1.38	2.4E-04	871
8	101635463	101636150	intron	ENST00000520661	SNX31	1.30	9.0E-05	687
13	114579128	114579433	promoter	ENST00000449453	RP11-199F6.4	1.33	2.3E-04	305
12	47488676	47488915	intron	ENST00000546455	PCED1B	1.53	9.5E-04	239
4	48946273	48946960	intergenic	ENST00000507399	RP11-317G22.2	-1.22	2.1E-05	687
17	40074968	40075633	promoter	ENST00000590735	ACLY	-1.00	4.9E-04	665
X	16804037	16805127	promoter	ENST00000398155	TXLNG	-1.12	2.1E-05	1090
15	102215274	102215634	intron	ENST00000539112	TARSL2	1.43	6.6E-04	360
16	88840365	88840766	intron	ENST00000301015	PIEZO1	1.47	1.5E-04	401
2	239835989	239836732	intergenic	ENST00000455228	AC114788.2	1.19	5.2E-04	743
2	129063639	129064276	intron	ENST00000494089	HS6ST1	1.06	6.7E-04	637
1	230994632	230995105	intron	ENST00000522201	C1orf198	1.59	4.5E-04	473
1	12100647	12101031	intergenic	ENST00000496974	RN7SL649P	1.01	7.1E-04	384
1	178877654	178877828	intron	ENST00000478871	RALGPS2	1.66	8.4E-04	174
17	15917197	15917706	intron	ENST00000497842	TTC19	1.20	7.6E-04	509
8	142157841	142158130	intron	ENST00000523015	DENND3	1.62	1.9E-04	289
10	121010086	121010469	intron	ENST00000392870	GRK5	1.31	2.5E-04	383
7	63212550	63212945	intergenic	ENST00000605464	CICP24	1.43	3.5E-05	395
12	131851320	131852149	promoter	ENST00000539209	RP13-507P19.1	1.52	5.6E-05	829
7	63217941	63218533	intergenic	ENST00000605464	CICP24	1.48	5.1E-05	592
5	40679080	40680306	promoter	ENST00000514343	PTGER4	-1.00	5.4E-07	1226
7	155199524	155200087	intergenic	ENST00000569431	RP5-912I13.1	1.59	6.7E-06	563
5	628422	629006	intron	ENST00000444221	CEP72	1.27	1.7E-04	584
17	81140434	81141322	intergenic	ENST00000572343	AC139099.4	1.21	6.6E-04	888
7	63216118	63216460	intergenic	ENST00000605464	CICP24	1.48	1.8E-04	342
17	105730	106265	intron	ENST00000570638	RPH3AL	1.38	1.2E-04	535
16	86878909	86879904	intergenic	ENST00000566109	RP11-107C10.1	1.25	3.6E-05	995
21	33157360	33157791	intergenic	ENST00000610276	AP000255.6	1.15	1.2E-04	431
11	22174396	22174976	intergenic	ENST00000530837	CTD-2019O4.1	-1.71	4.2E-08	580
16	33293693	33295127	intergenic	ENST00000573021	RP11-23E10.5	1.15	8.0E-04	1434

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
5	2490324	2490714	intergenic	ENST00000560688	RP11-129I19.2	1.13	1.5E-04	390
19	1164280	1165046	intron	ENST00000587655	SBNO2	1.01	5.2E-04	766
13	113680424	113680653	promoter	ENST00000473345	MCF2L	1.61	1.6E-04	229
14	60043166	60043680	promoter	ENST00000281581	CCDC175	-1.25	1.8E-04	514
18	34408158	34409506	promoter	ENST00000587139	KIAA1328	-1.07	1.1E-05	1348
17	55740045	55740953	intron	ENST00000579505	MSI2	-1.01	1.1E-05	908
17	44438927	44439708	promoter	ENST00000450673	ARL17B	-1.22	6.7E-04	781
7	206405	206816	intron	ENST00000477004	FAM20C	1.19	6.5E-04	411
7	63222975	63223858	intergenic	ENST00000605464	CICP24	1.12	5.0E-04	883
13	80055053	80055742	promoter	ENST00000457171	NDFIP2-AS1	-1.00	4.2E-04	689
4	40578882	40579574	intron	ENST00000513044	RBM47	-1.07	3.0E-08	692
9	140188004	140189043	promoter	ENST00000566954	RP13-122B23.8	-1.23	8.9E-04	1039
17	70613945	70614728	intron	ENST00000581549	LINC00511	-1.01	5.7E-06	783
5	74332978	74333338	intergenic	ENST00000322348	GCNT4	-1.09	4.2E-04	360
4	1722559	1723411	promoter	ENST00000536901	TMEM129	-1.03	1.4E-04	852
18	21166005	21167139	promoter	ENST00000540608	NPC1	-1.36	1.1E-09	1134
17	39058236	39058611	intergenic	ENST00000167588	KRT20	-1.19	5.7E-04	375
2	167231978	167233085	promoter	ENST00000375387	SCN9A	-1.12	1.6E-05	1107
Y	297421	298266	intergenic	ENST00000516032	RNU6-1334P	-1.02	5.9E-04	845
17	70462355	70462619	intron	ENST00000580861	LINC00511	-1.03	4.9E-06	264
22	42709789	42710226	intron	ENST00000515426	TCF20	-1.13	2.4E-04	437
13	30646504	30647236	intergenic	ENST00000413591	LINC00365	-1.28	4.7E-05	732
18	77393621	77394083	intergenic	ENST00000317008	RP11-567M16.3	1.02	8.3E-04	462
17	73613416	73613713	promoter	ENST00000578300	MYO15B	-1.09	4.0E-05	297
18	20558174	20558672	intron	ENST00000585177	RBBP8	-1.33	2.7E-07	498
21	18899540	18900000	promoter	ENST00000363884	Y_RNA	-1.31	8.0E-05	460
4	19557727	19558281	intron	ENST00000511431	RP11-608O21.1	-1.74	1.6E-06	554
4	99582947	99583241	exon	ENST00000569927_160528		-1.24	1.7E-04	294
15	102432818	102433991	intergenic	ENST00000560907	WBPILP5	1.21	2.1E-04	1173
3	195487289	195487523	intron	ENST00000480843	MUC4	1.63	6.1E-05	234
19	2128409	2128837	promoter	ENST00000590683	AP3D1	2.03	4.6E-07	428
4	156679791	156681400	promoter	ENST00000513437	GUCY1B3	-1.10	2.2E-06	1609
4	38735730	38736026	intergenic	ENST00000410298	RNA5SP158	1.17	5.5E-04	296
X	15755897	15756576	promoter	ENST00000380319	CA5B	-1.02	1.5E-04	679
19	51898699	51898961	promoter	ENST00000600765	CTD-2616J11.14	1.26	8.8E-04	262

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
4	103994568	103995223	intron	ENST00000508136	SLC9B2	-1.52	4.2E-05	655
2	241564963	241565884	promoter	ENST00000407714	GPR35	1.21	1.8E-05	921
4	7404260	7404679	intron	ENST00000329016	SORCS2	-1.76	1.7E-08	419
9	115851492	115852115	intergenic	ENST00000439875	FAM225B	1.39	2.6E-04	623
17	79486482	79486780	promoter	ENST00000442532	RP13-766D20.2	-1.29	2.9E-04	298
18	24159844	24160367	intron	ENST00000580191	KCTD1	-1.80	3.4E-06	523
13	21277892	21278693	promoter	ENST00000468605	IL17D	-1.14	2.2E-05	801
18	2654993	2656229	promoter	ENST00000579647	CBX3P2	-1.01	9.8E-04	1236
9	108081065	108081533	intron	ENST00000607692	SLC44A1	-1.33	1.4E-04	468
10	35838253	35839249	intron	ENST00000497692	CCNY	1.19	4.4E-04	996
18	3218007	3218215	promoter	ENST00000261606	MYOM1	-1.32	6.7E-04	208
16	32351227	32353593	intergenic	ENST00000562853	RP11-17M15.4	1.20	6.5E-05	2366
4	41992323	41992873	promoter	ENST00000510460	SLC30A9	-1.05	1.2E-05	550
4	122369404	122369799	intergenic	ENST00000512282	TUBB4BP5	-1.10	4.1E-04	395
18	6315695	6316404	intron	ENST00000580162	L3MBTL4	-2.14	3.8E-06	709
17	29816786	29817073	promoter	ENST00000578694	RAB11FIP4	-1.46	1.2E-07	287
17	38501710	38502341	promoter	ENST00000475125	RARA	-1.14	5.8E-05	631
13	35923722	35924281	intron	ENST00000379939	NBEA	-1.45	9.2E-04	559
13	103553441	103553830	intergenic	ENST00000605100	METTL21EP	-1.72	8.0E-05	389
4	62406648	62407173	intron	ENST00000514996	LPHN3	-1.51	4.9E-04	525
17	31281498	31281947	intergenic	ENST00000578289	TMEM98	-1.10	8.1E-05	449
8	134440828	134441594	intergenic	ENST00000393673	ST13P6	-1.33	3.1E-04	766
5	40784185	40784659	intron	ENST00000397006	PRKAA1	-1.24	2.1E-04	474
4	185269668	185270393	promoter	ENST00000511465	RP11-290F5.2	-1.12	1.4E-04	725
4	164471320	164471761	intron	ENST00000510786	1-Mar	-1.12	1.3E-05	441
17	45393737	45394013	intron	ENST00000575039	RP11-290H9.4	-1.59	1.3E-05	276
12	6873219	6873910	promoter	ENST00000540667	PTMS	-1.11	4.8E-04	691
1	201374557	201374865	exon	ENST00000361379_57596		-1.02	2.7E-05	308
22	41983726	41984326	promoter	ENST00000466645	PMM1	-1.17	8.3E-04	600
18	22067707	22067934	promoter	ENST00000583122	RP11-178F10.2	-1.13	6.5E-04	227
17	74392058	74392341	exon	ENST00000586409_558822		-1.21	2.0E-04	283
14	59296342	59296858	promoter	ENST00000555378	RP11-112J1.2	-1.17	1.0E-04	516
4	103701581	103701969	intergenic	ENST00000453744	UBE2D3	-1.03	5.8E-04	388
14	88715001	88715398	intron	ENST00000556282	KCNK10	-1.14	3.7E-04	397
4	57107532	57108067	intron	ENST00000264229	KIAA1211	-1.19	9.0E-04	535

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
18	52613423	52613785	intron	ENST00000587148	CCDC68	-1.13	4.0E-05	362
4	129495033	129495556	intergenic	ENST00000514265	RP11-184M15.1	-1.63	3.2E-06	523
10	112835917	112837154	promoter	ENST00000280155	ADRA2A	-1.34	9.1E-05	1237
X	7894985	7896017	promoter	ENST00000442940	PNPLA4	-1.21	4.6E-08	1032
2	183956117	183956559	intron	ENST00000444562	AC064871.3	-1.51	6.7E-04	442
18	71892391	71892807	promoter	ENST00000480810	RN7SL551P	-1.30	2.1E-04	416
6	2986172	2986575	promoter	ENST00000450238	LINC01011	-1.22	1.0E-04	403
14	38438045	38438416	intron	ENST00000533625	TTC6	-1.49	6.0E-04	371
4	30964479	30964886	intron	ENST00000509759	PCDH7	-1.41	5.2E-05	407
18	29740444	29740915	intron	ENST00000583696	GAREM	-1.99	5.7E-05	471
17	57069125	57069558	intron	ENST00000393066	TRIM37	-1.41	1.9E-07	433
12	105711706	105711997	intron	ENST00000549251	RP11-474B16.1	-1.49	3.2E-04	291
18	20284179	20284604	intron	ENST00000578831	RP11-739L10.1	-1.18	4.2E-05	425
17	64382980	64383423	intron	ENST00000284384	PRKCA	-1.24	1.5E-05	443
3	24640233	24640703	intergenic	ENST00000415266	EIF3KP2	-1.32	4.0E-04	470
18	14430668	14431655	intergenic	ENST00000584783	LONRF2P1	-1.04	9.7E-04	987
9	79249252	79250114	intron	ENST00000223609	PRUNE2	-1.81	4.8E-08	862
3	24565803	24566193	intergenic	ENST00000580344	MIR4792	-1.24	6.9E-04	390
4	108729691	108730105	intergenic	ENST00000506462	SGMS2	-1.23	3.2E-04	414
12	3982194	3982816	promoter	ENST00000450737	PARP11	-1.00	3.1E-04	622
14	50453931	50454479	intron	ENST00000530176	C14orf182	-1.02	2.7E-04	548
2	42422735	42423150	intron	ENST00000401738	EML4	-1.32	2.6E-04	415
8	8547367	8547711	intergenic	ENST00000519106	CLDN23	-1.14	1.6E-04	344
1	28648608	28649153	intergenic	ENST00000479574	MED18	-2.06	1.0E-07	545
12	646923	647267	intron	ENST00000535680	B4GALNT3	-1.24	4.0E-04	344
8	22222876	22223300	promoter	ENST00000359741	SLC39A14	-1.28	6.6E-04	424
5	162110217	162110778	intergenic	ENST00000517722	RP11-167P20.1	-1.85	3.0E-04	561
22	50228082	50228576	intron	ENST00000565177	RP3-522J7.6	-1.18	1.8E-04	494
12	1779737	1779986	intergenic	ENST00000577921	MIR3649	-1.41	3.7E-04	249
13	24758417	24758918	intron	ENST00000382141	RP11-307N16.6	-1.20	1.4E-04	501
4	187027154	187027446	promoter	ENST00000508379	FAM149A	-1.07	8.8E-05	292
4	149908119	149908467	intergenic	ENST00000458836	RNU7-197P	-1.05	8.7E-04	348
9	90184915	90185347	intron	ENST00000489291	DAPK1	-1.44	3.3E-04	432
4	154140059	154140489	intron	ENST00000338700	TRIM2	-1.62	9.8E-07	430
12	12556572	12557059	intron	ENST00000298571	LOH12CR1	-1.35	3.7E-04	487

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
4	37684752	37685026	intron	ENST00000454158	RELL1	-1.32	2.2E-04	274
17	62700725	62701052	intergenic	ENST00000604003	MINOS1P2	-1.42	8.0E-05	327
17	79823676	79823948	promoter	ENST00000576021	RP11-498C9.3	-1.24	6.2E-04	272
17	30533043	30533564	promoter	ENST00000581148	RHOT1	-1.01	5.9E-04	521
18	25185269	25185490	intergenic	ENST00000584546	RP11-739N10.1	-1.24	4.9E-04	221
18	2939329	2939618	intron	ENST00000261596	LPIN2	-1.42	9.6E-05	289
18	19774213	19774529	intron	ENST00000581694	GATA6	-1.46	9.2E-07	316
18	54937345	54938049	intergenic	ENST00000365370	RNU6-737P	-1.63	1.9E-04	704
3	191194228	191194546	intergenic	ENST00000518817	PYDC2	-1.75	2.5E-05	318
5	90184384	90184958	intron	ENST00000425867	GPR98	-1.05	2.7E-04	574
6	143160084	143160736	promoter	ENST00000367604	HIVEP2	-1.11	4.9E-04	652
18	30050445	30051372	promoter	ENST00000399218	GAREM	-1.53	2.7E-04	927
3	43255202	43255564	intergenic	ENST00000410399	AC104434.1	-1.35	1.8E-04	362
5	98360931	98361324	intergenic	ENST00000513175	CTD-2007H13.3	-1.26	4.8E-06	393
19	45198585	45199263	intron	ENST00000590796	CTB-171A8.1	-1.39	9.9E-05	678
17	76334969	76335254	intron	ENST00000586321	AC061992.2	-1.35	2.2E-06	285
3	24358451	24358695	intron	ENST00000418247	THRB	-1.11	3.7E-04	244
4	31148080	31148352	exon	ENST00000511884_155940		-1.70	1.2E-10	272
5	34212911	34213718	intron	ENST00000512782	RP11-1023L17.1	-1.68	2.1E-05	807
10	482220	483506	promoter	ENST00000425723	RP11-490E15.2	2.06	9.3E-04	1286
12	132060998	132062024	intergenic	ENST00000541343	RP11-292I17.1	2.01	2.0E-05	1026
20	61695692	61696532	intron	ENST00000607802	RP11-305P22.9	1.85	1.3E-04	840
4	7541341	7542231	intron	ENST00000329016	SORCS2	1.81	1.3E-04	890
16	88366497	88367260	intergenic	ENST00000563190	LA16c-444G7.1	1.32	2.6E-04	763
1	30664002	30664591	intergenic	ENST00000442774	RP3-357I16.1	1.41	2.7E-04	589
16	84558648	84558989	intron	ENST00000565079	TLDC1	1.67	6.6E-04	341
18	21453249	21453428	promoter	ENST00000587184	LAMA3	-1.37	2.1E-05	179
3	195542062	195542854	intergenic	ENST00000463781	MUC4	1.03	9.1E-04	792
15	29269492	29270164	promoter	ENST00000560531	RP13-126C7.1	1.12	4.0E-05	672
8	143026250	143026924	promoter	ENST00000408196	AC104417.1	1.21	6.0E-04	674
2	233755631	233756268	promoter	ENST00000461944	NGEF	1.49	2.4E-04	637
X	130712602	130713291	intergenic	ENST00000444577	OR13K1P	1.94	4.5E-05	689
2	242838585	242839046	intron	ENST00000429947	AC131097.3	1.12	1.5E-04	461
19	38943593	38944148	intron	ENST00000359596	RYR1	1.41	7.3E-05	555
19	50215579	50216042	promoter	ENST00000598072	CPT1C	1.61	4.9E-04	463

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
10	132897016	132897650	intron	ENST00000368642	TCERG1L	1.35	1.9E-04	634
18	3117490	3118235	intron	ENST00000261606	MYOM1	-1.48	4.7E-04	745
16	10394727	10395216	intergenic	ENST00000564797	ATF7IP2	1.47	3.0E-04	489
19	34112310	34112461	promoter	ENST00000591231	CHST8	1.65	6.3E-05	151
11	45149239	45150097	intron	ENST00000530656	PRDM11	1.11	4.1E-04	858
2	60524652	60525178	intergenic	ENST00000457668	AC007381.3	1.23	8.5E-04	526
18	19770500	19771301	intron	ENST00000581694	GATA6	-1.05	9.9E-05	801
2	3497474	3498028	intergenic	ENST00000607415	RP11-1293J14.1	1.49	8.0E-05	554
20	55201436	55201906	intergenic	ENST00000201031	TFAP2C	1.68	1.9E-04	470
19	39569172	39569875	intergenic	ENST00000601575	PAPL	1.42	2.7E-04	703
19	51893704	51894598	promoter	ENST00000570516	C19orf84	1.52	2.2E-04	894
10	133908226	133908803	intergenic	ENST00000298622	JAKMIP3	1.61	5.7E-06	577
17	44656868	44657529	promoter	ENST00000336125	ARL17A	-1.17	6.7E-04	661
7	101321102	101321282	intergenic	ENST00000223167	MYL10	1.54	5.7E-04	180
3	139289513	139290376	intron	ENST00000381790	RP11-319G6.1	1.22	6.6E-05	863
7	6116687	6117343	intergenic	ENST00000436915	AC004895.4	1.06	9.1E-05	656
1	117635514	117636236	promoter	ENST00000492682	TTF2	1.20	7.6E-04	722
12	132816724	132819336	intron	ENST00000328957	GALNT9	1.52	2.6E-04	2612
1	16005038	16005519	intergenic	ENST00000606262	RP4-680D5.9	1.45	1.1E-04	481
18	29522315	29523852	promoter	ENST00000580420	RP11-326K13.4	-1.51	8.6E-04	1537
1	17574935	17575827	promoter	ENST00000375460	PADI3	1.34	5.8E-04	892
9	104053040	104053880	intron	ENST00000463206	LPPR1	1.34	9.7E-04	840
15	80164774	80165510	intron	ENST00000494999	ST20-MTHFS	1.13	8.1E-05	736
20	44978838	44979690	exon	ENST00000493599_627499		1.19	5.6E-05	852
16	56641008	56641623	promoter	ENST00000245185	MT2A	1.21	3.2E-04	615
1	61105637	61106487	promoter	ENST00000439156	RP11-776H12.1	1.76	3.9E-06	850
9	139240060	139240754	intron	ENST00000354753	GPSM1	1.04	3.3E-04	694
16	53453058	53453761	intergenic	ENST00000567964	RBL2	1.22	5.7E-04	703
1	19724621	19725289	intron	ENST00000482808	CAPZB	1.45	1.7E-04	668
17	60266034	60266758	intergenic	ENST00000577881	RP11-51L5.3	-1.21	7.8E-05	724
19	52645300	52645902	promoter	ENST00000597886	CTC-471J1.9	1.26	1.9E-04	602
11	33202571	33203188	intron	ENST00000500025	CSTF3-AS1	1.21	7.8E-04	617
14	81769514	81770277	intron	ENST00000556280	STON2	-1.00	3.0E-06	763
11	9567258	9568184	intergenic	ENST00000396602	ZNF143	1.34	2.6E-04	926
5	34466571	34467442	intergenic	ENST00000503549	RP11-1325J9.1	-1.32	1.0E-09	871

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Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
2	237573927	237574674	intergenic	ENST00000455068	AC011286.1	1.18	8.6E-04	747
7	114670431	114671261	intergenic	ENST00000257724	MDFIC	1.48	6.6E-04	830
4	2420021	2420910	promoter	ENST00000382849	RP11-503N18.1	-1.03	6.5E-04	889
3	80745459	80745848	intergenic	ENST00000482003	RP11-47P18.1	-1.28	2.8E-06	389
4	125353676	125354469	intergenic	ENST00000506481	RP11-93J21.2	-1.10	2.8E-06	793
2	165477406	165478493	promoter	ENST00000446413	GRB14	-1.03	5.2E-04	1087
19	31899364	31900164	intron	ENST00000585336	AC007796.1	1.30	6.5E-04	800
20	45887465	45888265	intron	ENST00000468376	ZMYND8	1.10	4.6E-04	800
4	54342467	54343100	intron	ENST00000507166	FIPIL1	1.32	2.9E-04	633
1	25296870	25297681	promoter	ENST00000568143	RP11-84D1.2	1.02	6.3E-04	811
X	2815696	2816658	intergenic	ENST00000381154	ARSD	-1.22	2.8E-06	962
12	7950400	7950813	intergenic	ENST00000229307	NANOG	-1.42	1.7E-04	413
1	92791916	92792644	intron	ENST00000610020	RPAP2	1.20	5.9E-04	728
5	92414000	92415132	intergenic	ENST00000515153	CTD-2091N23.1	-1.04	2.9E-06	1132
11	70270264	70270605	promoter	ENST00000393747	CTTN	1.11	9.0E-04	341
18	24067372	24067793	intron	ENST00000578973	KCTD1	-1.42	3.2E-04	421
X	15692727	15694099	promoter	ENST00000380333	CASBP1	-1.05	1.8E-05	1372
3	195890536	195890927	intergenic	ENST00000457079	LINC00885	1.15	4.3E-04	391
10	133849722	133850635	intergenic	ENST00000368636	BNIP3	1.05	6.1E-05	913
1	29839867	29840197	intergenic	ENST00000515851	RP11-810H18.1	1.02	8.7E-04	330
12	132280700	132281100	promoter	ENST00000537582	SFSWAP	1.26	2.7E-04	400
4	120549649	120550511	promoter	ENST00000354960	PDE5A	-1.27	5.1E-07	862
5	60954962	60955315	exon	ENST00000505623_198864		-1.11	8.6E-04	353
8	107630045	107630587	promoter	ENST00000497705	OXR1	-1.06	4.7E-05	542
10	132892787	132893492	promoter	ENST00000436942	TCERGIL-AS1	1.17	2.2E-04	705
7	16961496	16961960	intergenic	ENST00000419352	AC098592.7	-1.21	2.5E-04	464
8	142597388	142597870	intergenic	ENST00000427937	AC138647.1	1.15	4.2E-05	482
4	125127833	125128704	intron	ENST00000507299	CTD-2325B11.1	-1.33	5.1E-05	871
2	233124653	233125150	exon	ENST00000433430_85344		1.04	4.0E-04	497
1	6305892	6306263	promoter	ENST00000377898	HES3	1.14	6.6E-04	371
X	47052740	47053352	promoter	ENST00000335972	UBA1	-1.22	6.5E-06	612
20	59832756	59833009	intron	ENST00000360469	CDH4	1.72	5.8E-04	253
5	87564239	87565285	promoter	ENST00000512724	TMEM161B-AS1	-1.06	5.2E-05	1046
4	124467237	124467606	intergenic	ENST00000508291	RP11-381N20.1	-1.29	4.6E-05	369
2	241811517	241811995	promoter	ENST00000476698	AGXT	1.47	1.3E-06	478

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
16	73116469	73116806	intergenic	ENST00000569990	HCCAT5	1.31	2.4E-04	337
16	32639949	32640460	intergenic	ENST00000564327	RP11-96K14.1	1.29	2.5E-04	511
7	151169967	151170459	promoter	ENST00000482053	RHEB	1.27	6.5E-04	492
15	59548285	59548587	intron	ENST00000558571	MYO1E	-1.06	2.4E-04	302
16	63651192	63652144	promoter	ENST00000563855	RP11-368L12.1	-1.25	5.9E-04	952
19	30154965	30155734	promoter	ENST00000436066	PLEKHF1	1.11	3.8E-06	769
7	5635384	5635656	promoter	ENST00000405801	FSCN1	1.01	7.3E-05	272
11	2008321	2008791	intron	ENST00000419080	MRPL23-AS1	1.26	3.8E-05	470
4	142271254	142271697	intergenic	ENST00000511213	RP11-362F19.1	-1.05	4.3E-04	443
X	7050318	7051134	intron	ENST00000498474	HDHD1	-1.08	1.8E-05	816
4	176986570	176987383	promoter	ENST00000280190	WDR17	-1.55	5.1E-05	813
3	15900398	15901920	promoter	ENST00000439830	ANKRD28	-1.06	4.2E-04	1522
18	21408398	21408763	promoter	ENST00000591749	LAMA3	-1.25	1.7E-06	365
4	36352766	36353045	intron	ENST00000504344	RP11-431M7.2	-1.08	1.8E-04	279
4	26828299	26828789	intergenic	ENST00000494628	STIM2	-1.12	5.5E-04	490
19	34760796	34761482	intron	ENST00000585833	KIAA0355	1.04	1.6E-05	686
3	188506277	188507139	intron	ENST00000459897	LPP	1.01	3.1E-04	862
17	36507408	36508157	promoter	ENST00000577233	SOCS7	-1.02	2.2E-05	749
4	149297345	149297623	intron	ENST00000511528	NR3C2	-1.19	5.8E-04	278
19	38538873	38540260	intron	ENST00000476317	SIPA1L3	1.19	3.3E-04	1387
12	17795043	17795272	intergenic	ENST00000539105	RP11-606D9.1	-1.30	8.9E-06	229
11	64512396	64512888	promoter	ENST00000377485	RASGRP2	1.12	6.7E-04	492
18	77679919	77680340	intron	ENST00000478144	PQLC1	1.18	5.5E-04	421
5	156692779	156693779	promoter	ENST00000517634	CTC-248O19.1	-1.15	8.9E-07	1000
19	38524195	38525390	intron	ENST00000476317	SIPA1L3	1.46	2.0E-04	1195
18	21452574	21453145	promoter	ENST00000587184	LAMA3	-1.60	8.0E-11	571
19	36760064	36760513	intergenic	ENST00000355114	ZNF565	1.43	9.9E-04	449
4	90226929	90227192	promoter	ENST00000609438	GPRIN3	-1.34	7.6E-05	263
16	4464103	4464762	promoter	ENST00000576457	CORO7	-1.03	5.3E-04	659
X	24482963	24483767	promoter	ENST00000441463	PDK3	-1.15	2.0E-06	804
18	12657581	12658532	promoter	ENST00000400512	AP005482.1	-1.10	6.7E-04	951
7	534134	534368	promoter	ENST00000434541	AC147651.1	1.29	7.7E-07	234
7	30829073	30829346	intron	ENST00000451002	INMT-FAM188B	1.25	4.4E-04	273
5	70743142	70743357	promoter	ENST00000502659	RP11-136K7.2	-1.14	7.6E-04	215
3	195510841	195511431	exon	ENST00000478156_152007		1.25	9.4E-04	590

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
4	54457506	54458027	promoter	ENST00000512247	LNK1	-1.07	9.4E-06	521
16	4394345	4394677	promoter	ENST00000575848	PAM16	1.18	4.0E-04	332
10	11927228	11927674	intron	ENST00000445498	PROSER2-AS1	1.49	3.1E-04	446
22	43892550	43892910	intron	ENST00000538182	MPPED1	1.12	3.3E-04	360
9	114827947	114828604	intron	ENST00000374264	SUSD1	-1.39	1.0E-04	657
20	59950361	59951203	intron	ENST00000360469	CDH4	1.05	5.7E-04	842
17	72987700	72988299	intron	ENST00000337231	CDR2L	-1.01	2.0E-04	599
17	62161429	62162290	intron	ENST00000584041	ERN1	-1.17	5.3E-05	861
18	20263110	20263735	intergenic	ENST00000578831	RP11-739L10.1	-1.58	3.4E-08	625
20	31208975	31209164	intergenic	ENST00000360785	C20orf203	1.39	1.7E-04	189
7	158995289	158995591	intergenic	ENST00000437005	PIP5K1P2	1.27	5.3E-04	302
8	17658296	17659254	promoter	ENST00000522768	RP11-156K13.1	-1.23	3.1E-04	958
19	1144620	1144966	intron	ENST00000587655	SBNO2	1.32	8.2E-04	346
2	97117403	97117850	intergenic	ENST00000310865	NEURL3	1.02	1.3E-04	447
1	245100328	245100603	intergenic	ENST00000364888	RN7SKP55	1.66	1.0E-04	275
19	38735536	38736387	promoter	ENST00000590510	SPINT2	1.49	2.8E-04	851
19	34809126	34810741	intron	ENST00000588338	KIAA0355	1.38	7.8E-06	1615
17	854896	856177	intron	ENST00000575171	NXN	1.26	2.9E-04	1281
19	31830912	31831630	intron	ENST00000558569	TSHZ3	1.69	4.6E-04	718
19	38905395	38905919	promoter	ENST00000588708	RASGRP4	1.69	5.2E-05	524
13	30122775	30123280	intron	ENST00000450494	SLC7A1	-1.31	2.2E-04	505
3	152974102	152975125	intergenic	ENST00000582522	RN7SL300P	1.04	4.6E-04	1023
17	56494818	56495318	promoter	ENST00000580014	RNF43	-1.02	1.8E-04	500
12	15427333	15427966	intron	ENST00000393736	RERG	-1.30	1.0E-05	633
18	19862218	19863030	intergenic	ENST00000459476	snoU13	-1.39	6.3E-06	812
14	31697679	31698056	intergenic	ENST00000365532	Y_RNA	-1.23	7.5E-05	377
20	55363228	55363724	intergenic	ENST00000384429	RNU6-929P	1.55	1.6E-06	496
19	36799597	36800084	promoter	ENST00000600983	CTD-3162L10.1	1.36	8.1E-04	487
19	31828906	31829306	intron	ENST00000558569	TSHZ3	1.46	3.1E-04	400
4	79548832	79549112	intergenic	ENST00000364128	Y_RNA	-1.04	8.0E-04	280
1	148929648	148931757	promoter	ENST00000457390	RP11-14N7.2	1.14	5.7E-04	2109
16	57298954	57299312	promoter	ENST00000564018	PLLP	-1.09	1.7E-07	358
18	20679542	20679947	intergenic	ENST00000400473	CABLES1	-1.17	2.1E-05	405
12	12223581	12224233	promoter	ENST00000308721	BCL2L14	-1.13	2.6E-04	652
5	170224689	170225199	intron	ENST00000519598	GABRP	1.03	2.0E-04	510

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
8	118958604	118959299	intron	ENST00000436216	EXT1	-1.00	6.4E-04	695
5	170184196	170184589	promoter	ENST00000521965	MIR4454	-1.23	1.2E-05	393
15	39565852	39566905	promoter	ENST00000561058	RP11-624L4.1	-1.14	1.8E-08	1053
5	81931049	81932003	intergenic	ENST00000510845	CTD-2015A6.2	-1.01	2.7E-04	954
1	8800026	8800575	intron	ENST00000480342	RERE	1.26	8.8E-04	549
14	87265459	87266198	intergenic	ENST00000557527	RP11-322L20.1	-1.35	8.6E-04	739
4	169019178	169019931	intron	ENST00000506926	RP11-310I9.1	-1.29	1.3E-06	753
1	165742556	165743015	exon	ENST00000423121_23045		1.33	7.8E-04	459
1	180126329	180127241	intron	ENST00000367600	QSOX1	-1.08	4.7E-04	912
3	195627548	195627967	intron	ENST00000468819	TNK2	1.01	8.7E-04	419
1	68345690	68346295	intron	ENST00000413628	GNG12-AS1	-1.11	1.1E-04	605
5	95429064	95430289	intron	ENST00000511775	CTD-2337A12.1	-1.22	6.0E-05	1225
12	113342092	113342931	promoter	ENST00000202917	OAS1	1.04	9.7E-04	839
14	50908246	50909117	intron	ENST00000013125	MAP4K5	-1.07	4.0E-05	871
16	56687942	56688603	intergenic	ENST00000334346	MT1B	1.20	9.2E-04	661
4	98353586	98354125	intron	ENST00000518105	RP11-681L8.1	-1.30	8.0E-05	539
X	17613238	17614124	intron	ENST00000380060	NHS	-1.26	3.9E-04	886
7	86475603	86476697	intron	ENST00000439827	GRM3	-1.30	5.4E-04	1094
13	73745224	73745935	intergenic	ENST00000364383	RNU4-10P	-1.20	9.9E-05	711
13	39260761	39261550	promoter	ENST00000280481	FREM2	-1.21	2.3E-10	789
1	11999122	11999719	intron	ENST00000196061	PLOD1	1.23	9.4E-04	597
18	14178703	14179225	promoter	ENST00000581181	ANKRD20A5P	-1.32	1.2E-05	522
6	15949256	15950233	intergenic	ENST00000448802	ARPC3P5	-1.21	3.3E-04	977
5	73704005	73704568	intron	ENST00000507781	CTC-419K13.1	-1.18	2.1E-05	563
4	184276391	184276972	intergenic	ENST00000514910	RP11-451F20.1	-1.10	3.7E-04	581
18	29952163	29952949	intron	ENST00000269209	GAREM	-1.80	1.2E-05	786
4	120651110	120651691	intergenic	ENST00000503266	RP11-236P13.1	-1.15	8.8E-06	581
4	147866860	147867427	promoter	ENST00000502319	TTC29	-1.10	5.1E-05	567
13	24606606	24607289	intron	ENST00000382141	RP11-307N16.6	-1.27	4.9E-06	683
9	116333099	116333705	intron	ENST00000428429	RP11-168K11.2	-1.05	1.5E-04	606
16	52288281	52288983	promoter	ENST00000408588	AC007333.1	-1.15	9.5E-04	702
4	168139291	168139787	intron	ENST00000512042	SPOCK3	-1.35	6.0E-04	496
2	237791572	237792049	intergenic	ENST00000413385	AC011286.1	1.28	2.9E-04	477
1	4016604	4017089	intergenic	ENST00000412674	RP13-614K11.1	1.09	4.1E-04	485
5	50728721	50729673	intergenic	ENST00000505723	CTD-2335O3.2	-1.01	1.4E-04	952

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
10	14862005	14862511	intron	ENST00000465530	CDNF	1.30	9.5E-04	506
4	111751532	111751971	intergenic	ENST00000515999	AC024198.1	-1.22	6.6E-04	439
X	64416588	64417229	intergenic	ENST00000451184	RP11-231N9.1	-1.05	3.8E-04	641
1	227947119	227947769	intron	ENST00000478768	SNAP47	1.30	6.6E-05	650
13	76583584	76584230	intergenic	ENST00000448806	LINC01034	-1.58	7.1E-05	646
18	21207297	21207674	intron	ENST00000587763	ANKRD29	-1.54	1.3E-08	377
22	32475114	32475693	intron	ENST00000543737	SLC5A1	-1.52	4.1E-07	579
3	126678871	126679767	intron	ENST00000510044	CHCHD6	1.17	1.3E-06	896
4	106830892	106831539	promoter	ENST00000506056	NPNT	-1.21	7.1E-06	647
15	63343399	63343882	promoter	ENST00000561241	RP11-244F12.3	-1.35	4.6E-05	483
3	141133388	141134001	intron	ENST00000513570	ZBTB38	1.28	9.2E-04	613
21	36391861	36392371	intron	ENST00000416754	RUNX1	-1.14	4.7E-04	510
13	103782751	103783563	intergenic	ENST00000245312	SLC10A2	-1.43	2.0E-05	812
5	110072468	110072845	promoter	ENST00000512886	TMEM232	-1.09	1.4E-04	377
9	89951812	89952262	intergenic	ENST00000391119	SNORA26	-1.23	7.0E-08	450
18	8794410	8794963	intron	ENST00000518815	SOGA2	-1.63	6.2E-05	553
10	79115617	79115970	promoter	ENST00000418515	RP11-619F23.2	1.10	6.8E-04	353
17	48770069	48771000	promoter	ENST00000574246	RP11-294J22.6	-1.21	9.2E-05	931
5	14581642	14582228	promoter	ENST00000274217	FAM105A	-1.12	2.4E-05	586
18	71007537	71008213	intron	ENST00000583942	CTD-2354A18.1	-1.40	7.0E-04	676
22	34142384	34142996	intron	ENST00000416275	LARGE-AS1	-1.32	4.7E-04	612
19	51596977	51597664	intergenic	ENST00000421832	CTU1	1.06	8.0E-04	687
18	7878650	7879298	intron	ENST00000400053	PTPRM	-1.20	1.8E-04	648
4	67440362	67441524	intergenic	ENST00000470993	RPS23P3	-1.27	3.6E-08	1162
11	68847695	68848373	intron	ENST00000442692	TPCN2	1.11	3.5E-05	678
15	86106408	86107073	intron	ENST00000558811	AKAP13	-1.08	1.4E-04	665
14	38063747	38065628	promoter	ENST00000556845	TTC6	-1.08	4.5E-07	1881
13	74864507	74864895	promoter	ENST00000383890	RNY1P5	-1.55	6.9E-04	388
22	40783623	40784186	promoter	ENST00000607915	RP5-1042K10.10	-1.27	4.5E-04	563
18	23669906	23671402	promoter	ENST00000578595	SS18	-1.27	4.1E-05	1496
2	228626684	228627219	promoter	ENST00000516537	RNA5SP121	-1.67	2.7E-04	535
14	75749392	75750562	intergenic	ENST00000303562	FOS	-1.27	3.2E-06	1170
5	34717596	34718270	promoter	ENST00000502736	RAH14	1.03	1.4E-04	674
1	204616727	204616979	intron	ENST00000496057	LRRN2	1.14	1.1E-04	252
9	132105932	132106561	promoter	ENST00000423122	RP11-65J3.1	1.05	3.0E-04	629

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
19	7489776	7490370	intron	ENST00000593531	CTD-2207O23.3	-1.17	1.7E-04	594
X	21816665	21817660	intergenic	ENST00000465888	MBTPS2	-1.03	6.1E-04	995
9	131821742	131822331	promoter	ENST00000474639	FAM73B	1.16	9.9E-04	589
18	60087362	60088390	promoter	ENST00000591796	RP11-640A1.4	-1.02	1.3E-05	1028
2	187426114	187426881	intergenic	ENST00000261023	ITGAV	1.22	1.6E-05	767
18	21269015	21270342	promoter	ENST00000399516	LAMA3	-1.15	8.2E-10	1327
8	26165314	26165833	intron	ENST00000523964	PPP2R2A	-1.10	3.8E-04	519
6	43663358	43663937	intergenic	ENST00000372133	MRPS18A	-1.39	5.1E-06	579
10	8610021	8610921	intergenic	ENST00000425516	CHCHD3P1	-1.01	7.6E-04	900
10	52753171	52754401	intron	ENST00000373985	PRKG1	-1.13	1.3E-05	1230
17	69325178	69326441	intergenic	ENST00000410631	RNU6-305P	-1.35	2.1E-05	1263
12	22741552	22742171	intergenic	ENST00000535801	RP11-268P4.2	-1.66	1.6E-05	619
4	77613059	77614188	intron	ENST00000486758	SHROOM3	-1.47	8.2E-06	1129
22	42579385	42580044	intron	ENST00000404876	TCF20	-1.28	4.7E-04	659
11	102800546	102801385	intergenic	ENST00000260302	MMP13	-1.15	5.5E-05	839
1	168769107	168770153	intergenic	ENST00000420691	LINC00626	-1.51	3.6E-04	1046
17	48968048	48968736	intron	ENST00000514358	TOB1-AS1	-1.42	8.2E-09	688
6	131579205	131579893	intron	ENST00000474850	AKAP7	-2.08	9.6E-06	688
5	111869063	111869538	intergenic	ENST00000514243	RP11-159K7.1	-1.05	2.7E-05	475
10	9866325	9867152	intergenic	ENST00000419836	RP5-1051H14.2	-1.51	4.2E-04	827
21	40174479	40175013	intergenic	ENST00000360214	ETS2	-1.48	1.0E-04	534
3	169022989	169023782	intron	ENST00000485957	MECOM	-1.09	1.3E-04	793
10	74209572	74210383	intron	ENST00000489666	MICU1	-1.48	9.2E-04	811
2	101441977	101442437	intron	ENST00000430586	AC092168.2	-1.65	2.1E-05	460
15	71438884	71439471	intron	ENST00000261862	THSD4	-1.30	6.6E-04	587
18	52434366	52434770	intron	ENST00000586570	RAB27B	-1.67	1.4E-06	404
X	17027964	17029048	intron	ENST00000380064	REPS2	-1.40	4.7E-05	1084
4	74889262	74890088	intergenic	ENST00000464637	RN7SL218P	-1.21	4.3E-04	826
8	127836689	127837275	intergenic	ENST00000519319	PCAT1	-1.41	3.6E-14	586
5	60757258	60757764	intron	ENST00000252744	ZSWIM6	-1.20	6.5E-05	506
3	151576923	151578197	intron	ENST00000475855	RP11-454C18.2	-1.62	1.9E-04	1274
X	17050088	17050991	intron	ENST00000380064	REPS2	-1.22	4.1E-05	903
15	54081718	54082628	intergenic	ENST00000383914	RNU6-449P	-1.63	3.1E-04	910
4	115433283	115434630	intergenic	ENST00000310836	UGT8	-1.23	6.4E-06	1347
6	131579943	131580553	intron	ENST00000474850	AKAP7	-1.61	5.7E-07	610

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
7	65226259	65226827	promoter	ENST00000384058	SNORA15	-1.65	3.5E-05	568
12	22715040	22716069	intergenic	ENST00000542742	RP11-359J14.3	-1.65	1.9E-06	1029
8	8543551	8544101	intergenic	ENST00000519106	CLDN23	-1.53	3.8E-05	550
17	56477290	56477780	intron	ENST00000583841	BZRAP1-AS1	-1.09	9.2E-05	490
4	30903182	30904207	intron	ENST00000511884	PCDH7	-1.09	1.8E-05	1025
12	13539722	13539939	promoter	ENST00000532841	C12orf36	-1.34	4.5E-04	217
12	13539993	13540519	promoter	ENST00000531049	C12orf36	-1.34	8.7E-05	526
4	109875916	109876470	intron	ENST00000399126	COL25A1	-1.34	2.7E-04	554
15	97862475	97863361	promoter	ENST00000559394	RP11-315L6.1	-1.52	4.7E-04	886
5	32302570	32303291	intron	ENST00000513622	MTMR12	-1.36	4.6E-04	721
15	30110396	30110856	intron	ENST00000473741	TJP1	-1.14	2.9E-04	460
4	175181121	175181620	intron	ENST00000513696	FBXO8	-1.43	4.1E-05	499
21	16513635	16514425	intergenic	ENST00000449746	AF127577.12	-1.38	2.9E-05	790
2	66800612	66801208	promoter	ENST00000433396	AC007392.3	-1.41	5.1E-04	596
3	169097224	169097849	intron	ENST00000485957	MECOM	-1.23	1.3E-05	625
4	149352458	149353065	intron	ENST00000511528	NR3C2	-1.02	9.1E-04	607
7	116452899	116453499	promoter	ENST00000464223	CAPZA2	-1.44	9.7E-06	600
12	122595449	122596247	intron	ENST00000319080	MLXIP	-1.04	9.3E-04	798
X	110580244	110580776	intron	ENST00000496551	DCX	-1.33	6.6E-04	532
6	56558773	56559190	promoter	ENST00000521104	DST	-1.14	8.2E-04	417
8	71578881	71579614	promoter	ENST00000276590	LACTB2	-1.09	2.1E-04	733
14	31503002	31503435	intron	ENST00000555417	AP4S1	-1.35	3.1E-07	433
5	55053665	55054839	intron	ENST00000504880	SLC38A9	-1.45	2.7E-05	1174
14	68631120	68631904	intron	ENST00000557045	RAD51B	-1.19	9.1E-04	784
4	53728083	53728700	promoter	ENST00000515677	RASL11B	-1.00	3.4E-05	617
X	17878644	17879810	promoter	ENST00000545871	RAI2	-1.24	4.3E-04	1166
17	31121546	31122070	intron	ENST00000583621	MYO1D	-1.43	6.7E-04	524
13	73899238	73900358	intergenic	ENST00000420129	MARK2P12	-1.07	2.2E-04	1120
7	117356474	117357412	intron	ENST00000445366	CTTNBP2	-1.10	3.5E-04	938
17	71856589	71857110	intergenic	ENST00000580370	CTD-2532D12.5	-1.05	9.1E-04	521
4	87863404	87863696	intron	ENST00000511442	AFF1	-1.14	1.0E-04	292
14	90114844	90115344	promoter	ENST00000516846	Y_RNA	-1.33	6.3E-04	500
13	113339543	113340006	intergenic	ENST00000356049	C13orf35	-1.43	4.0E-04	463
18	20714210	20714563	promoter	ENST00000579963	CABLES1	-1.18	7.2E-05	353
13	106458613	106459355	intergenic	ENST00000415294	LINC00343	-1.09	4.0E-04	742

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
18	10798713	10799240	intron	ENST00000579112	PIEZO2	-1.31	2.7E-05	527
4	154110178	154111052	intron	ENST00000437508	TRIM2	-1.00	4.2E-04	874
15	74305515	74306058	intron	ENST00000564725	PML	-1.73	6.2E-04	543
5	60550923	60551655	intron	ENST00000503882	CTC-436P18.3	-1.45	5.6E-06	732
10	60228227	60229121	intergenic	ENST00000373886	BICC1	-1.33	9.2E-05	894
2	151828282	151829233	intergenic	ENST00000425983	AC023469.2	-1.10	9.5E-05	951
4	156625042	156625531	intron	ENST00000513574	GUCY1A3	-1.16	1.8E-05	489
16	82061215	82061820	intergenic	ENST00000563491	HSD17B2	-1.53	4.5E-06	605
3	27683392	27684170	intergenic	ENST00000607601	RP11-222K16.1	-1.08	4.7E-04	778
8	38624299	38625022	intron	ENST00000348567	TACC1	-1.03	8.6E-05	723
17	46018633	46019210	promoter	ENST00000433001	AC003665.1	-1.15	2.2E-04	577
5	139544548	139545540	exon	ENST00000607850_189600		-1.20	3.2E-04	992
4	30954382	30954826	intron	ENST00000509759	PCDH7	-1.17	5.2E-04	444
X	35457520	35458562	intergenic	ENST00000516602	RNU6-1087P	-1.06	2.0E-04	1042
8	17652219	17652783	intron	ENST00000381862	MTUS1	-1.53	5.6E-05	564
1	172137033	172137953	intron	ENST00000523513	DNM3	-1.28	9.8E-04	920
4	155664739	155665500	promoter	ENST00000510733	LRAT	-1.59	1.9E-14	761
22	39317071	39317566	promoter	ENST00000450216	CTA-150C2.13	-1.00	3.0E-04	495
11	22696063	22696714	promoter	ENST00000433790	GAS2	-1.36	2.2E-06	651
5	66381100	66381787	intron	ENST00000447738	MAST4	-1.09	1.3E-04	687
4	45648854	45650096	intergenic	ENST00000363850	RNU6-931P	-1.02	2.8E-04	1242
4	187564825	187565498	intron	ENST00000441802	FAT1	-1.40	5.3E-07	673
15	53746791	53747925	intergenic	ENST00000567224	WDR72	-1.40	5.0E-05	1134
4	105862880	105863326	intron	ENST00000515649	RP11-556I14.1	-1.11	7.2E-04	446
4	77521435	77522140	intron	ENST00000485780	SHROOM3	-1.13	7.2E-04	705
1	160512233	160512642	exon	ENST00000534968_54273		-1.54	1.4E-04	409
4	25789258	25790342	intron	ENST00000502949	SEL1L3	-1.49	6.0E-05	1084
21	15588231	15588966	promoter	ENST00000400577	RBM11	-1.36	4.0E-05	735
15	23095116	23095978	promoter	ENST00000559762	RP11-566K19.5	-1.14	6.8E-05	862
10	3598428	3598998	intergenic	ENST00000426811	RP11-482E14.2	1.87	5.3E-04	570
12	43309649	43310455	intergenic	ENST00000603420	RP11-510P12.1	-1.26	3.0E-04	806
2	36008748	36009185	intergenic	ENST00000431951	MRPL50P1	-1.81	2.2E-04	437
4	175547466	175548242	intergenic	ENST00000274093	GLRA3	-1.43	1.7E-04	776
12	123129219	123129801	intron	ENST00000356987	HCAR1	1.17	3.5E-04	582
8	42082268	42083254	promoter	ENST00000459183	snoU13	-1.26	5.4E-04	986

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
5	139598938	139599611	intron	ENST00000509789	CYSTM1	-1.22	5.5E-04	673
7	121037949	121038214	promoter	ENST00000411715	CYCSP19	-1.35	9.2E-07	265
4	94763615	94764289	intergenic	ENST00000306011	ATOH1	-1.26	2.5E-04	674
12	12603953	12604650	promoter	ENST00000605743	RP11-253I19.4	-1.48	8.2E-04	697
18	21075012	21075330	intergenic	ENST00000269221	C18orf8	-1.19	3.7E-04	318
X	23925684	23926349	promoter	ENST00000490078	APOO	-1.02	8.0E-05	665
21	36250878	36251125	intron	ENST00000486278	RUNX1	-1.32	7.2E-04	247
18	8329209	8329564	intron	ENST00000577827	PTPRM	-1.19	1.4E-04	355
2	73944031	73944360	intergenic	ENST00000489476	TPRKB	-1.29	2.2E-06	329
4	37491862	37492339	intron	ENST00000508175	C4orf19	-1.21	5.4E-05	477
Y	2558421	2558773	intergenic	ENST00000516032	RNU6-1334P	-1.32	9.6E-05	352
15	63969949	63970349	promoter	ENST00000559715	HERC1	-1.11	4.9E-04	400
18	19664513	19664896	intergenic	ENST00000579830	RP11-595B24.2	-1.15	4.9E-07	383
4	74548559	74549428	intergenic	ENST00000436089	AC112518.3	-1.19	4.1E-04	869
18	9422752	9423417	intergenic	ENST00000262120	TWSG1	-1.51	3.5E-04	665
18	21464667	21465113	promoter	ENST00000586751	LAMA3	-1.31	6.7E-05	446
4	48261077	48261668	intron	ENST00000381501	TEC	-1.28	8.2E-05	591
12	15305835	15306272	promoter	ENST00000541243	RERG-AS1	-1.21	5.5E-05	437
4	105979088	105979826	intron	ENST00000506386	RP11-556I14.1	-1.08	4.5E-04	738
X	2608934	2609490	promoter	ENST00000381180	CD99	-1.44	9.0E-07	556
13	73544410	73545113	promoter	ENST00000469712	PIBF1	-1.58	1.1E-06	703
4	55896756	55897737	promoter	ENST00000517006	RNU6-410P	-1.39	1.6E-04	981
4	13703459	13704075	intron	ENST00000510907	RP11-341G5.1	-1.31	3.2E-05	616
14	64137369	64137812	intergenic	ENST00000247225	SGPP1	-1.71	4.0E-04	443
12	26421726	26422408	intron	ENST00000540392	RP11-283G6.4	-1.37	8.2E-05	682
18	4004111	4004976	promoter	ENST00000582051	DLGAP1	-1.51	3.5E-04	865
X	16328282	16328968	intergenic	ENST00000516839	AC078993.1	-1.31	2.9E-04	686
X	13012317	13012875	intergenic	ENST00000451311	TMSB4X	-1.75	2.4E-05	558
5	50521576	50522552	intergenic	ENST00000468490	CTD-2312P21.1	-1.06	1.1E-04	976
4	87933836	87934323	intron	ENST00000544085	AFF1	-1.28	1.1E-04	487
15	57619201	57619605	promoter	ENST00000567319	RP11-358M11.4	-1.29	1.4E-04	404
8	118959719	118960347	intron	ENST00000436216	EXT1	-1.20	9.7E-05	628
4	170106361	170107215	intron	ENST00000508685	SH3RF1	-1.55	6.5E-06	854
14	23029755	23030313	intergenic	ENST00000557595	AE000662.92	-1.03	2.5E-05	558
13	102392011	102392599	intron	ENST00000376143	FGF14	-1.38	5.2E-04	588

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
4	186639663	186640609	intron	ENST00000456060	SORBS2	-1.17	2.3E-04	946
17	35281035	35281678	intron	ENST00000529264	RP11-445F12.1	-1.22	1.8E-05	643
18	19790101	19790813	intergenic	ENST00000578741	RP11-627G18.4	-1.43	2.0E-07	712
4	85432843	85433341	intergenic	ENST00000295886	NKX6-1	-1.15	5.1E-04	498
1	40357889	40358640	intergenic	ENST00000397332	MYCL	-1.30	7.4E-05	751
13	52532098	52532856	intron	ENST00000542656	ATP7B	-1.03	7.5E-05	758
12	92940036	92940836	promoter	ENST00000459090	snoU13	-1.50	7.6E-05	800
4	158954507	158955331	intergenic	ENST00000513850	RP11-312A15.3	-1.07	2.3E-06	824
X	132843583	132844339	intron	ENST00000406757	GPC3	-1.88	1.5E-05	756
5	31048491	31049119	intergenic	ENST00000495944	RPL19P11	-1.19	4.2E-04	628
18	24337137	24337871	intron	ENST00000579964	AQP4-AS1	-1.32	5.9E-04	734
4	151435655	151436697	intron	ENST00000513021	LRBA	-1.10	6.8E-04	1042
4	72003550	72004695	intergenic	ENST00000264485	SLC4A4	-1.27	2.5E-04	1145
16	52290147	52290849	promoter	ENST00000408588	AC007333.1	-1.27	1.0E-04	702
18	19624260	19625733	intron	ENST00000584898	RP11-595B24.1	-1.37	3.1E-07	1473
18	21209345	21209877	promoter	ENST00000587763	ANKRD29	-1.41	3.0E-10	532
13	102399458	102399928	intron	ENST00000376143	FGF14	-1.68	3.8E-06	470
4	106772105	106772882	intron	ENST00000510876	INTS12	-1.11	2.2E-04	777
18	21290854	21291433	promoter	ENST00000588044	RPL23AP77	-1.41	5.1E-05	579
13	108486621	108487030	promoter	ENST00000449551	FAM155A-IT1	-1.35	5.9E-04	409
8	135029476	135029978	intergenic	ENST00000605278	RP11-157E21.2	-1.27	5.8E-04	502
13	73614637	73615691	intergenic	ENST00000437000	PSMD10P3	-1.09	3.1E-04	1054
18	60766821	60767604	intergenic	ENST00000398117	BCL2	-1.01	1.8E-04	783
9	27385265	27386040	intron	ENST00000603061	MOB3B	-1.31	3.5E-04	775
17	72970801	72971274	promoter	ENST00000532900	HID1	-1.29	2.8E-04	473
X	24163828	24164250	intergenic	ENST00000427551	ZFX-AS1	-1.95	1.9E-06	422
18	70985941	70986635	intergenic	ENST00000563172	CTD-2354A18.1	-1.61	3.1E-04	694
12	9880385	9880890	intron	ENST00000327839	CLECL1	-1.33	8.1E-04	505
13	60181712	60182550	intergenic	ENST00000400324	DIAPH3	-1.26	6.9E-05	838
15	90877324	90877942	intergenic	ENST00000412799	GABARAPL3	-1.17	2.2E-04	618
18	59402679	59403762	intron	ENST00000590968	RP11-879F14.1	-1.28	8.2E-04	1083
14	39308853	39309445	promoter	ENST00000557440	LINC00639	-1.08	1.4E-04	592
4	22943322	22944138	intergenic	ENST00000511453	RP11-412P11.1	-1.16	7.5E-04	816
4	139833077	139833445	intron	ENST00000507038	RP11-371F15.3	-1.03	2.4E-04	368
18	19686422	19686904	intergenic	ENST00000579830	RP11-595B24.2	-1.11	6.5E-06	482

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
10	43137085	43137382	intergenic	ENST00000486614	ZNF33B	-1.35	2.5E-04	297
20	15119226	15119713	intron	ENST00000310348	MACROD2	-1.51	5.0E-07	487
21	36168889	36169428	intron	ENST00000399240	RUNX1	-1.09	9.0E-04	539
18	4017582	4018096	intron	ENST00000577430	DLGAP1	-1.26	7.7E-04	514
5	132208952	132209463	promoter	ENST00000485457	LEAP2	-1.25	7.5E-04	511
7	115979679	115980039	intron	ENST00000446355	AC002066.1	-1.22	4.9E-04	360
18	55102256	55103165	promoter	ENST00000581316	AC090340.1	-1.02	3.1E-04	909
4	170035695	170036113	intron	ENST00000284637	SH3RF1	-1.61	1.7E-04	418
X	15872339	15873736	promoter	ENST00000421527	AP1S2	-1.09	2.1E-08	1397
4	177114274	177114599	promoter	ENST00000515234	SPATA4	-1.69	2.3E-04	325
18	40105871	40106286	intron	ENST00000589068	LINC00907	-1.40	7.3E-04	415
13	99300363	99300982	intergenic	ENST00000430810	CALM2P4	-1.25	1.6E-04	619
7	12969053	12969525	intergenic	ENST00000441256	RBMX2P4	-1.31	3.5E-04	472
X	117907769	117908146	intron	ENST00000371637	IL13RA1	-1.28	2.2E-04	377
1	12050437	12051116	intron	ENST00000412236	MFN2	1.27	8.3E-04	679
4	171147427	171147816	intergenic	ENST00000504509	RP11-789C1.1	-1.58	8.7E-04	389
12	13158692	13159059	intron	ENST00000543321	RP11-377D9.3	-1.66	2.7E-04	367
8	29595979	29596739	intron	ENST00000506121	LINC00589	-1.10	3.4E-05	760
8	22312699	22313062	intron	ENST00000522000	PPP3CC	-1.41	2.6E-04	363
4	103811017	103811934	intron	ENST00000514972	SLC9B1	-1.11	5.3E-04	917
8	8549498	8549897	intergenic	ENST00000519106	CLDN23	-1.38	3.2E-04	399
4	106818891	106819676	promoter	ENST00000513430	NPNT	-1.04	7.7E-04	785
10	6343519	6344014	intron	ENST00000399868	RP11-563J2.2	-1.02	2.6E-04	495
9	78528856	78529314	promoter	ENST00000459505	AL359253.1	-1.59	9.4E-06	458
5	17114415	17114792	intron	ENST00000606445	BASP1	-1.06	3.2E-04	377
X	15624226	15624853	intron	ENST00000421585	GS1-594A7.3	-1.44	5.7E-04	627
18	21189439	21189988	intron	ENST00000591617	ANKRD29	-1.54	1.6E-05	549
10	115312349	115312929	promoter	ENST00000541666	HABP2	-1.19	9.3E-04	580
6	119915982	119916519	intergenic	ENST00000368468	MAN1A1	-1.26	8.3E-04	537
19	39646961	39647663	promoter	ENST00000599657	PAK4	1.28	2.7E-04	702
4	157873335	157873855	intron	ENST00000422544	PDGFC	-1.58	3.2E-04	520
4	77510524	77510923	intron	ENST00000485780	SHROOM3	-1.06	2.6E-04	399
3	7246159	7246840	intron	ENST00000435689	GRM7	-1.25	7.7E-04	681
18	9673064	9673873	intergenic	ENST00000581937	KRT18P8	-1.16	5.7E-04	809
18	71068317	71068856	intergenic	ENST00000563172	CTD-2354A18.1	-1.22	8.9E-04	539

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Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
4	18814749	18815500	intergenic	ENST00000503815	RP11-608B3.1	-1.54	6.5E-04	751
18	9736984	9737287	promoter	ENST00000578806	RP11-692N5.2	-1.58	7.5E-04	303
12	21597079	21597766	intron	ENST00000538582	PYROXD1	-1.38	7.6E-05	687
18	28981489	28981834	promoter	ENST00000581452	RP11-534N16.1	-1.56	5.4E-04	345
5	37165920	37166523	intron	ENST00000511824	C5orf42	-1.15	1.4E-04	603
12	60566172	60566790	intergenic	ENST00000551882	RP11-335M9.1	-1.26	6.7E-04	618
18	26372413	26372889	intergenic	ENST00000582726	RP11-510D21.1	-1.30	1.3E-04	476
X	3631095	3632157	promoter	ENST00000262848	PRKX	-1.25	2.1E-06	1062
18	3250757	3251051	promoter	ENST00000578562	MYL12A	-1.05	8.9E-04	294
18	65288323	65288979	intron	ENST00000583687	RP11-638L3.1	-1.51	4.2E-04	656
5	144843814	144844163	intergenic	ENST00000510259	PRELID2	-1.41	1.0E-04	349
18	21544367	21545241	intron	ENST00000582300	RP11-403A21.1	-1.06	4.2E-04	874
12	71557965	71558303	intron	ENST00000549421	TSPAN8	-1.61	1.8E-04	338
12	13025022	13026103	intergenic	ENST00000459725	RPL13AP20	-1.09	2.5E-04	1081
12	71555389	71555659	intron	ENST00000549421	TSPAN8	-1.60	5.5E-04	270
5	54660393	54660916	intron	ENST00000545714	SKIV2L2	-1.16	7.1E-04	523
6	106894847	106895225	intergenic	ENST00000365516	RNA5SP211	-1.80	2.0E-04	378
X	77192772	77193146	intron	ENST00000602791	RP5-1000K24.2	-1.23	2.4E-04	374
18	12000289	12000722	promoter	ENST00000588863	IMPA2	-2.16	3.4E-05	433
18	3456781	3457062	promoter	ENST00000472042	TGIF1	-1.75	3.1E-05	281
5	43893907	43894383	intergenic	ENST00000508829	RP11-8L21.1	-1.61	1.2E-04	476
13	35515748	35516975	promoter	ENST00000379939	NBEA	-1.58	3.8E-11	1227
18	26374435	26374857	intergenic	ENST00000582726	RP11-510D21.1	-1.31	2.1E-04	422
15	89668375	89668644	intron	ENST00000562073	ABHD2	-1.65	2.6E-04	269
4	37978642	37979668	promoter	ENST00000446803	TBC1D1	-1.06	6.4E-05	1026
13	77498752	77499091	intergenic	ENST00000426582	BTF3P11	-1.37	8.4E-04	339
X	105961933	105962318	intron	ENST00000324342	RNF128	-1.51	9.7E-04	385
14	56355837	56356276	intergenic	ENST00000569625	RP11-1012E15.1	-1.08	3.5E-04	439
3	66543117	66543471	intron	ENST00000475366	LRIG1	-1.23	1.5E-04	354
4	4501198	4501552	intron	ENST00000512780	STX18	-1.44	8.4E-04	354
15	90401815	90402255	intron	ENST00000559629	C15orf38-AP3S2	-1.93	2.5E-05	440
7	13005419	13005842	intergenic	ENST00000441256	RBMX2P4	-1.15	2.6E-04	423
14	37798337	37798669	intron	ENST00000556940	MIPOL1	-1.52	6.7E-06	332
17	48774453	48774711	promoter	ENST00000364470	Y_RNA	-1.16	6.7E-04	258
13	32519681	32520190	intron	ENST00000428783	EEF1DP3	-1.12	7.1E-06	509

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Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
17	10640501	10640980	intron	ENST00000583012	CTC-297N7.5	-1.12	5.2E-05	479
8	142140988	142141629	promoter	ENST00000517908	RP11-809O17.1	1.23	3.7E-04	641
9	45008582	45009082	intron	ENST00000421848	RP11-374M1.4	-1.17	6.0E-04	500
18	19748853	19749787	promoter	ENST00000583490	GATA6-AS1	-1.54	1.0E-06	934
8	17646298	17647375	intron	ENST00000381862	MTUS1	-1.20	5.7E-04	1077
17	618801	619322	promoter	ENST00000437048	VPS53	-1.27	6.7E-04	521
13	93125967	93126657	intron	ENST00000377067	GPC5	-1.64	6.0E-04	690
10	65479061	65479739	intron	ENST00000444770	RP11-170M17.1	-1.72	1.2E-06	678
3	19189370	19190217	promoter	ENST00000452398	KCNH8	-1.61	1.6E-05	847
1	59245356	59246066	intergenic	ENST00000371222	JUN	-1.23	4.7E-05	710
9	105629671	105630230	intergenic	ENST00000430854	RP11-338N12.1	-1.50	3.7E-04	559
2	134946547	134947309	intron	ENST00000409645	MGAT5	-1.11	8.1E-04	762
12	113905094	113906232	intron	ENST00000261731	LHX5	1.03	7.6E-04	1138
13	78271260	78272125	promoter	ENST00000466548	SLAIN1	-1.58	4.6E-08	865
14	68658282	68659082	intron	ENST00000557045	RAD51B	-1.08	4.4E-05	800
X	22003441	22003730	intron	ENST00000415881	SMS	-1.08	1.9E-04	289
7	38903200	38903772	intron	ENST00000457055	VPS41	-1.16	4.2E-06	572
17	53510366	53511001	intergenic	ENST00000262065	MMD	-1.11	1.7E-04	635
3	194353440	194353664	promoter	ENST00000447139	AC046143.3	1.07	8.2E-04	224
12	15373831	15374573	promoter	ENST00000537717	RERG	-1.02	2.1E-05	742
15	52199610	52200183	promoter	ENST00000606352	U6	-1.12	2.3E-08	573
Y	2476943	2477666	intergenic	ENST00000516032	RNU6-1334P	-1.19	1.4E-04	723
17	46024345	46024764	promoter	ENST00000580372	RP11-6N17.6	-1.16	9.1E-04	419
X	1710260	1710695	promoter	ENST00000381261	AKAP17A	-1.01	6.7E-04	435
Y	2558832	2559585	intergenic	ENST00000516032	RNU6-1334P	-1.33	8.4E-07	753
18	23806089	23807166	promoter	ENST00000418698	TAF4B	-1.39	2.7E-05	1077
4	69598563	69599228	intergenic	ENST00000509261	RP11-1267H10.4	-1.31	9.2E-08	665
12	6419391	6420221	promoter	ENST00000396988	PLEKHG6	-1.05	4.5E-04	830
18	2984812	2985290	promoter	ENST00000584915	LPIN2	-1.58	6.0E-05	478
X	20392961	20393546	intergenic	ENST00000517169	RN7SKP183	-1.03	8.9E-04	585
15	66124847	66125582	intron	ENST00000568850	RAB11A	-1.07	6.5E-06	735
4	119273882	119274465	promoter	ENST00000296498	PRSS12	-1.00	5.3E-05	583
3	19188141	19189179	promoter	ENST00000328405	KCNH8	-1.13	2.3E-04	1038
11	94335540	94336653	intron	ENST00000537874	RP11-867G2.8	-1.14	1.1E-05	1113
18	29665492	29665879	intron	ENST00000583184	RP11-5316.2	-1.70	2.9E-04	387

Table 1								
Chr	Start	End	Annotation	Transcript ID	Gene symbol	Fold Change	P-value (adj)	Peak width (bp)
5	176513355	176514471	promoter	ENST00000513166	FGFR4	-1.02	2.6E-04	1116
18	12376764	12377928	promoter	ENST00000590811	AFG3L2	-1.05	4.2E-04	1164
X	33780627	33780788	intron	ENST00000445233	RP11-305F18.1	-1.32	9.7E-04	161
X	83441953	83443818	promoter	ENST00000460730	RPS6KA6	-1.04	1.3E-04	1865
4	15679072	15679693	intron	ENST00000514541	FBXL5	-1.30	6.6E-10	621
3	194432537	194433012	intron	ENST00000423318	AC090505.6	1.01	6.1E-04	475
17	36070163	36070788	intron	ENST00000560016	HNF1B	-1.79	6.3E-11	625
18	28551397	28551656	intron	ENST00000583580	RP11-25I11.1	-1.93	8.6E-05	259
18	21795580	21796435	promoter	ENST00000384039	RNU6-435P	-1.00	9.5E-04	855
4	89897580	89898181	intron	ENST00000509094	FAM13A	-1.15	9.6E-04	601
8	40013191	40014286	intergenic	ENST00000315792	C8orf4	-1.03	3.5E-04	1095
4	52883991	52884363	promoter	ENST00000343457	LRRC66	-1.30	2.6E-04	372
3	66692481	66692862	intergenic	ENST00000459863	RPL21P41	-1.43	8.0E-04	381
18	19748357	19748632	promoter	ENST00000579431	GATA6-AS1	-1.26	1.8E-04	275
5	58145773	58146112	intron	ENST00000510198	CTD-2176I21.2	-1.35	1.2E-05	339
5	40485204	40485821	intergenic	ENST00000583717	AC108105.1	-1.22	2.4E-04	617
7	64532350	64532740	promoter	ENST00000384334	SNORA15	-1.70	6.4E-06	390
18	21450963	21451245	promoter	ENST00000269217	LAMA3	-1.41	1.8E-07	282
15	57899754	57900281	intron	ENST00000569089	MYZAP	-1.17	1.9E-06	527
12	27425172	27426386	intron	ENST00000543246	STK38L	-1.11	2.0E-05	1214
2	306486	306655	promoter	ENST00000592090	AC079779.5	1.89	9.5E-05	169
16	83983871	83984533	promoter	ENST00000361711	OSGIN1	1.35	7.1E-05	662
7	591580	592225	promoter	ENST00000517177	AC147651.2	1.23	1.8E-04	645
Median								595.5
Min.								151
Max.								2612

8.2 EXAMPLE 2: qPCR Array methodology

8.2.1 ATAC-qPCRarray Preparation:

[00283] ATAC-qPCRarray platform technology was developed in order to cross-validate the chromatin accessibility signature (as obtained by ATAC-seq as described in Example 1 above) classifying PDAC patients into recurrent and non-recurrent groups.

[00284] An array was prepared on a desired format. The array was prepared by taking the coordinates of previously identified open chromatin peaks, the start and end loci.

[00285] Oligonucleotide primers were designed which are complementary to these open chromatin regions (between the start and the end loci) to amplify the specific targeted region of the chromatin accessible regions. A set of oligonucleotide primers targeting a specific open chromatin region was placed in a PCR amplification plate on an array format (FIGs. 4A-4B) as described in Example 2. One or more sets of oligonucleotide primers may target a specific open chromatin region.

[00286] An exemplary PDAC array may target fewer than 100 chromatin regions identified in Table 1 and/or Table 2.

Table 2				
Chromosome	Start	End	Annotation	Symbol
chr12	19,426,717	19,427,323	Intron	<i>PLEKHA5</i>
chr3	105,525,021	105,525,647	Intron	<i>CBLB</i>
chr2	145,077,946	145,078,518	Intron	<i>GTDC1</i>
chr4	40,674,840	40,675,527	Intergenic	<i>RBM47</i>
chr5	110,062,076	110,062,896	Promoter	<i>TMEM232</i>
chr9	75,766,438	75,767,040	Promoter	<i>ANXA1</i>
chr4	81,094,544	81,094,954	Intergenic	<i>PRDM8</i>
chr13	74,289,467	74,290,340	Intron	<i>KLF12</i>
chr7	35,762,586	35,763,101	Intergenic	<i>LOC100506725</i>
chr7	7,984,167	7,984,977	Intergenic	<i>GLCC11</i>
chr12	76,371,552	76,372,217	Intergenic	<i>PHLDA1</i>
chr4	101,960,452	101,960,971	Intron	<i>PPP3CA</i>
chr2	145,140,347	145,140,933	Intergenic	<i>GTDC1</i>
chr6	135,889,386	135,889,933	Intron	<i>LINC00271</i>
chr3	109,523,484	109,524,020	Intergenic	<i>MIR4445</i>
chr3	105,465,536	105,466,279	Intron	<i>CBLB</i>
chr4	36,256,926	36,257,681	Promoter	<i>LOC439933</i>
chr3	189,042,301	189,043,047	TTS	<i>TPRG1</i>
chr11	85,534,713	85,535,433	Intergenic	<i>SYTL2</i>
chr13	99,871,034	99,871,786	Intron	<i>UBAC2</i>
chr7	143,072,243	143,073,098	Intergenic	<i>FAM131B</i>
chr5	58,419,377	58,419,920	Intron	<i>PDE4D</i>
chr6	128,292,926	128,293,807	Intron	<i>PTPRK</i>
chr2	161,250,545	161,251,085	Intron	<i>RBMS1</i>
chr13	74,600,816	74,601,467	Intron	<i>KLF12</i>

Table 2				
Chromosome	Start	End	Annotation	Symbol
chr2	137,084,604	137,085,454	Intergenic	<i>CXCR4</i>
chr3	71,542,455	71,543,074	Intron	<i>FOXP1</i>
chr1	192,485,704	192,486,501	Intergenic	<i>RGS1</i>
chr14	20,801,062	20,801,767	Promoter	<i>CCNB1IP1</i>
chr4	102,448,189	102,448,931	Intergenic	<i>FLJ20021</i>
chr10	6,540,520	6,541,245	Intron	<i>PRKCQ</i>
chr1	183,602,686	183,603,277	Intron	<i>ARPC5</i>
chr18	60,087,645	60,088,463	Intergenic	<i>TNFRSF11A</i>
chr14	70,082,213	70,082,726	Intron	<i>SUSD6</i>
chr5	50,006,858	50,007,607	Intron	<i>PARP8</i>
chr4	114,468,552	114,469,125	Exon	<i>CAMK2D</i>
chr6	137,710,174	137,710,795	Intergenic	<i>OLIG3</i>
chr5	67,575,735	67,576,365	Intron	<i>PIK3R1</i>
chr1	66,815,639	66,816,413	Intron	<i>PDE4B</i>
chr1	84,944,781	84,945,643	Intron	<i>RPF1</i>
chr8	134,315,289	134,316,163	Intergenic	<i>NDRG1</i>
chr6	143,223,647	143,224,367	Intron	<i>HIVEP2</i>
chr7	130,920,376	130,920,953	Intron	<i>MKLN1</i>
chr6	130,004,960	130,005,621	Intron	<i>ARHGAP18</i>
chr10	81,082,715	81,083,458	Intergenic	<i>PPIF</i>
chr4	122,859,782	122,860,343	Intron	<i>TRPC3</i>
chr12	90,343,531	90,344,571	TTS	<i>LINC02399</i>
chr2	161,284,266	161,284,976	Intron	<i>RBMS1</i>
chr6	36,409,032	36,409,598	Intron	<i>PXT1</i>
chr13	41,593,129	41,593,701	Promoter	<i>ELF1</i>
chr6	138,132,378	138,132,988	Intergenic	<i>TNFAIP3</i>
chr8	116,660,226	116,660,896	Intron	<i>TRPS1</i>
chr8	91,639,845	91,640,621	Intron	<i>TMEM64</i>
chr3	95,424,587	95,425,386	Intergenic	<i>MTHFD2P1</i>
chr12	92,754,202	92,754,753	Intergenic	<i>CLLU1</i>
chr7	92,250,105	92,250,723	Intron	<i>CDK6</i>
chr3	111,386,503	111,387,218	Intergenic	<i>PLCXD2</i>
chr5	25,569,096	25,569,799	Intergenic	<i>LINC02211</i>
chr3	150,102,582	150,103,090	Intergenic	<i>TSC22D2</i>
chr12	75,904,898	75,905,901	Promoter	<i>KRR1</i>
chr3	112,709,379	112,710,528	Exon	<i>GTPBP8</i>
chr11	14,436,552	14,437,156	Intergenic	<i>RRAS2</i>
chr6	106,642,940	106,643,882	Intron	<i>ATG5</i>

Table 2				
Chromosome	Start	End	Annotation	Symbol
chr3	183,003,467	183,004,223	Intron	<i>MCF2L2</i>
chr4	104,020,729	104,021,363	Promoter	<i>BDH2</i>
chr2	162,164,500	162,165,398	5' UTR	<i>PSMD14</i>
chr6	131,520,609	131,521,624	Intron	<i>AKAP7</i>

8.2.2. Library Preparation:

[00287] ATAC libraries were prepared as described in detail below. Briefly, intact nuclei were extracted from a biological sample. A Tn5 transposase complex was added to the intact nuclei. Following an incubation, transposed DNA fragments were extracted from the reaction solution and amplified to provide ATAC libraries.

[00288] The preparation of tumor specimens followed the procedure outlined below: first EpCAM+ PDAC malignant cells, or CD8+ T-lymphocytes were isolated from the tumor and peripheral blood respectively, and then ATAC-libraries were made (the details of the methodology in given below).

8.2.2.1 Making single-cell suspension from PDAC FNA/laparoscopic surgical/surgically resected specimens:

[00289] The FNA/laparoscopic surgical/surgically resected specimens were taken into a 50-ml Gentle-MACS "C" tube containing the digestion buffer: 5 ml of media (MEM+ protease inhibitor) + 100µl of liberase (Roche) + 50µl P188 (15mM stock) + 5µl DNase-1 (10mg/ml stock) + 37.5µl CaCl₂ (1M stock) and the tube was placed in Gentle-MACS tissue dissociator machine for 60 min at 37°C. After incubation, 5 ml of MACS buffer was added, and the suspension filtered through 40µM filter (BD cell strainer) into another 50 ml microfuge tube. The tube was centrifuged @500xg for 5 min at 4°C and the supernatant discarded. 500µL of ACK lysing buffer was added to the pellet, incubated for 5 min at RT then diluted immediately with 4.5 ml of MACS buffer (BSA diluted 1:20 with Auto-MACS rinsing solution). The tube was centrifuged @500xg for 5 min at 4°C and the supernatant discarded. The cell pellet was re-suspended in 50µL of MACS buffer and 50 µL of FcR Blocking Reagent and 50 µL of CD326 (EpCAM) Micro-Beads were added. The mixture was mixed well and refrigerated for 30 minutes (4–8°C) but not on ice. After the incubation, the cells were washed once by adding 5 ml of MACS buffer and centrifuged at 500xg for 5 minutes at 4°C. The supernatant was aspirated completely. The pellet was re-suspended in 500µL of MACS buffer and proceed to magnetic separation.

8.2.3. Magnetic separation of EpCAM+ cells with LS Columns

[00290] A 15 ml tube was used for collection of the effluents (start preparing the column by rinsing with 3ml MACS buffer while centrifuging the cell suspension). The cell suspension 500 μ L was applied onto the column. “Unlabeled” cells (anything other than epithelial cells) that pass through were collected and the column was washed with 3x3ml of buffer as effluent. Washing steps were performed by adding buffer three times. The column was removed from the separator and placed on a 15ml collection tube. 5ml of buffer was pipetted onto the column. The magnetically labeled cells were flushed out by firmly pushing the plunger into the column. (To increase the purity of the magnetically labeled fraction, the cells may be passed over a new, freshly prepared column.) The cells (~5 ml total suspension) were pelleted down @500xg for 5 min at 4°C. The unlabeled cells (~12.5ml total suspension from previous step) were also pelleted down @500xg for 5 min at 4°C. Supernatant was discarded and labeled cells were re-suspended in 200 μ L of 1X cold PBS. The cells were counted, and only epithelial cells fraction were used for ATAC-library preparation utilizing 10,000 – 50,000 cells, and the remaining cells were stored for DNA/RNA extraction (later with Qiagen All-prep DNA-RNA kit). The “Effluent” fraction was pelleted down and stored at -80°C along with the epithelial cell fraction for future DNA/RNA extraction in order to utilize it as control for checking epithelial enrichment.

8.2.4. Continue with transposition reaction on the isolated cells

[00291] 10,000-50,000 cells were taken in each of the two 1.5 ml microfuge tubes (in duplicates) and centrifuged for 5 min at 500 $\times$ g at 4°C. Supernatant was discarded and the cell pellet was re-suspended by pipetting up and down in 50 μ L of cold lysis buffer. The re-suspended pellet was centrifuged immediately for 10 min at 500 $\times$ g at 4°C. This step affords lysis of cells with nonionic detergent and generated a crude nuclei preparation. The supernatant was discarded, and the crude nuclei preparation was used in the transposition reaction.

8.2.5. Transposition reaction and purification

[00292] Transposition reaction and purification were performed as described in Buenrostro, *Nat Methods* (2013) with modifications. The cell pellet was placed on ice. Transposition reaction mixture:

- a. In 100- μ L for a duplicate library reaction:
 - i. 50- μ L TN5 buffer TD (2 $\times$ reaction buffer from Nextera kit)

- ii. 45-μL nuclease-free water
- iii. 5-μL TN5 enzyme TDE1 (Nextera Tn5 Transposase from Nextera kit)
- b. The transposition reaction mixture was incubated at 37°C for 30 min with gentle mixing to increase fragment yield.

[00293] The transposition reaction mixture was incubated at 37°C for 30 min with gentle mixing to increase fragment yield. Purification was performed using The transposition reaction mixture was eluted in 20-μL elution buffer (Qiagen MinElute PCR Purification Kit) before PCR. Purified DNA was stored at –20°C if necessary.

7.3.6. PCR amplification of transposed DNA fragments

[00294] 10-μL elute was taken into the 50-μL PCR-reaction and then the usual protocol was followed with the primer pairs as described in Buenrostro, *Nat Methods* (2013) (supplement). The amplicons were purified with Qiagen mini-elute PCR cleanup kit.

[00295] The following was combined in a 0.2 ml PCR tube:

- 10μl transposed DNA (or the cleaned product of the first PCR)
- 10μl nuclease-free H₂O
- 2.5μl 25μM PCR Primer 1
- 2.5μl 25μM Barcoded PCR Primer 2 (1 through 24– all primers, forward (primer 1) and reverse (primer 2) from Buenrostro, *Nat Methods* (2013) (supplement)
- 25μl NEBNext High-Fidelity 2× PCR Master Mix

[00296] Primers and PCR conditions were optimized for amplifying large-molecular-weight fragments from low-input material. Integrated DNA Technologies (IDT) synthesized all primers – with no additional modifications. Samples were barcoded appropriately for subsequent pooling and sequencing.

[00297] Thermal cycle conditions were as follows:

1 cycle:	5 min	72°C
	30 sec	98°C
12 cycles:	10 sec	98°C

30 sec 63°C

1 min 72°C.

[00298] The first 5-min extension at 72°C allowed for extension of both ends of the primer after transposition, thereby generating amplifiable fragments.

[00299] Amplified library was purified using Qiagen MinElute PCR Purification Kit. The purified library was eluted in 20µl elution buffer (Buffer EB from the MinElute kit consisting of 10mM Tris·Cl, pH 8). The column was dried prior to adding elution buffer to avoid ethanol contamination in the final library. Typically, the nanodrop concentration after 12 cycle PCR is ~10 fold more than the before PCR (The concentration of DNA eluted from the column ought to be approximately 30nM; however, 5-fold variation is possible and not detrimental). The quality of purified libraries was assessed using a Bioanalyzer High-Sensitivity DNA Analysis kit (Agilent).

7.3.7. qPCR of the libraries with the qPCRarray

[00300] The ATAC-qPCR-array will be made by selected differentially represented regions and that will be normalized with control regions. Typically, control regions are ACRs that exhibit no significant or detectable differential expression between the two phenotypes of comparison. No Template Control (n) will be used as negative control. The specific set of oligonucleotide primers will be designed using publicly available Primer 3 software. The primers will be optimized and the sequence of each amplicon will be confirmed by Sanger sequencing. The set of optimized primers will be used to make the ATAC-qPCRarrays using 96-well or 384-well format (as displayed in FIGs. 4A-4B). The set of test regions will be selected based on the differentially represented ACRs between two phenotypic groups, e.g., poor versus good prognosis, or responder versus non-responder groups of patients to a certain therapy (e.g., chemotherapy, targeted therapy, or immunotherapy). Quantitative measurement of target accessible region relative to control regions will be performed in triplicates using Power SYBR Green PCR Master Mix (Applied Biosystems, Warrington, UK cat # 4368706) following the manufacturer's recommendations. Relative quantitation of the chromatin accessibility will be defined by $2^{-\Delta Ct}$, where $\Delta Ct = Ct_{\text{target region}} - Ct_{\text{control region}}$. A score will be assigned to each patient based on the relative quantitation of the ACRs by the ATAC-qPCR array.

8.3 EXAMPLE 3- ATAC-qPCRarray for evaluating PDAC recurrence

[00301] Biological samples (e.g., surgically resected tumors, tumor biopsy, liquid biopsy, circulating shedding tumor cells, circulating tumor DNA) are collected from patients who may be at risk, diagnosed, or suspected of having pancreatic ductal adenocarcinoma (PDAC). The samples are processed for extraction of RNA, optionally and DNA. cDNA samples are generated as described in Example 2 or using conventional methods. The cDNA samples are used as template for amplification of accessible chromatic regions (ACRs) identified in Examples 1 and 2, and quantified by quantitative PCR (qPCR). A set of oligonucleotide probes for targeting differentiated phenotypes (e.g., risk of early recurrence of PDAC) are designed. Each set of oligonucleotide probes include a subset of primers targeting a first phenotype, and a subset of primers targeting a second phenotype. At least one set (e.g., 2, 3, 4, 5, or more) of qPCR primers for each phenotype are designed using publicly available Primer 3 software. The set of primers are designed for targeting 1-100 ACRs associated with recurrent of PDAC as described in Table 1 and/or Table 2, or in FIG. 5. Typically, the set of primers are designed to amplify DNA fragments of no more than 100 bp (e.g., 40-100 bp). Each pair of qPCR primers are placed onto a PCR amplification plate in an array format as shown in FIGs. 4A-4B. The qPCR amplification products are quantified and normalized. Statistical analyses are as described in Example 2. The results show the patient's risk of early recurrence.

8.4 EXAMPLE 4-ATAC-qPCRarray for predicting response to immunotherapy

[00302] Biological samples (e.g., surgically resected tumors, tumor biopsy, liquid biopsy, circulating shedding tumor cells, circulating tumor DNA) are collected from patients who may be at risk, diagnosed, or suspected of having pancreatic ductal adenocarcinoma (PDAC). The samples are processed for extraction of RNA, optionally and DNA. cDNA samples are generated as described in Example 2 or using conventional methods. The cDNA samples are used as template for amplification of accessible chromatic regions (ACRs) identified in Examples 1 and 2, and quantified by quantitative PCR (qPCR). At least one set (e.g., 2, 3, 4, 5, or more) of qPCR primers for each phenotype are designed using publicly available Primer 3 software. A set of oligonucleotide probes for targeting differentiated phenotypes (e.g., sensitivity to immunotherapy) are designed. Each set of oligonucleotide probes include a subset of primers targeting a first phenotype, and a subset of primers targeting a second phenotype. The set of primers are designed for targeting 1-100 ACRs associated with sensitivity to immune checkpoint inhibitor therapy (e.g., anti-PD1, anti-PD-L1, nivolumab, pembrolizumab) of PDAC as described in Table 1 and/or Table 2, or in FIG. 5. Typically, the set of

primers are designed to amplify DNA fragments of no more than 100 bp (e.g., 40-100 bp). Each pair of qPCR primers are placed onto a PCR amplification plate in an array format as shown in FIGs. 4A-4B. The qPCR amplification products are quantified and normalized. Statistical analyses are as described in Example 2. The results show the patient’s sensitivity to immune checkpoint inhibitor therapy and provides assessment for efficacy of personalized immune checkpoint inhibitor therapy.

8.5 EXAMPLE 5 - Identification of ATAC-qPCR Array targets using Least Absolute Shrinkage and Selection Operator (LASSO)

[00303] Ten iterations of 5-fold cross validation were performed within glmnet and the average of the lambda values was chosen as the optimal lambda to control for randomization. Then, for every model, the features with non-zero coefficients were saved and finally compared with the ones resulting from the final model. As a sanity check, the frequency of the features in every iteration’s glmnet model was checked and only the features (from the final model) repeating in every single model were chosen as the final results. We used the ATAC-array input data of 49 pancreatic cancer patients with known outcomes (disease-free survival (DFS) following surgery and adjuvant chemotherapy with Gemcitabine/ Nab-Paclitaxel) as the training set analyses. Since microarray data are prone to missing values, ATAC-array input data of all 49 patients was filtered for missing values for certain regions before feeding it into the model. Survival data including disease free survival (DFS) and recurrence status of all the 49 patients were used in the model. The following arguments were used as input for the model: *family* of “Cox” was used, *type.measure* was set as “C” or Harrel’s concordance measure was used for loss of cross-validation, *alpha* value was set to 1, *standardize* argument which controls the variable standardization prior to fitting the model sequence was set to TRUE.

[00304] The LASSO model resulted in 12 ACRs. Four constitutive ACRs, as described below, were used as controls for normalization of the differential regions. The ACRs were classified as either “blue” regions, or “red” regions, or “green” regions. The “blue” regions indicate the ACRs which are open in patients with good prognosis but silenced (closed) in patient with poor prognosis with Gemcitabine/Nab-Paclitaxel chemotherapy.

[00305] Table 3 provides 12 differential and 4 control ACRs identified by analysis in silico.

Table 3. Differential and control ACRs identified by analysis in silico					
Chr	Start	End	HUGO symbol	Classification	Length (bp)
chr19	4084177	4084702	MAP2K2	red	525

Table 3. Differential and control ACRs identified by analysis in silico					
Chr	Start	End	HUGO symbol	Classification	Length (bp)
chr1	56933904	56934476	PPAP2B	red	572
chr8	1878704	1879351	ARHGEF10	blue	647
chr3	128914473	128915151	CNBP	red	678
chr6	110064994	110065287	FIG4	red	293
chr17	15917197	15917706	TTC19	red	509
chr8	8547367	8547711	CLDN23	blue	344
chr19	39569172	39569875	PAPL	red	703
chr3	152974102	152975125	RN7SL300P	red	1023
chr2	187426114	187426881	ITGAV	red	767
chr12	13539993	13540519	C12orf36	blue	526
chr4	177114274	177114599	SPATA4	blue	325
chr6	111279570	111280284	GTF3C6	ctrl	714
chr1	226270679	226271550	LINC01703	ctrl	871
chr1	231376653	231377603	C1orf131	ctrl	950
chr7	152372887	152373496	XRCC2	ctrl	609

[00306] A prognostic score (PS) was assigned to each patient based on these 18 differentially accessible chromatin regions following the formula:

Prognostic score (PS) by ATAC-array = (median of blue – median of red)/median of control green

[00307] Based on the PS calculated in each patient by this 12-chromatin accessibility signature, patients were segregated by PS values more than and less than the median value respectively, and then analyzed by Cox regression of proportional hazards. FIG. 6 is a K-M graph showing a significant segregation with Log Rank p value=0.0019.

8.5.5. Identification of the internal control regions

[00308] Intersection analysis of constantly accessible genomic regions from ATAC-Seq data was performed by BEDOPS tool –element-of command (Neph et al., BEDOPS: high-performance genomic feature operations. Bioinformatics. 2012 Jul 15;28(14):1919-20.) to identify internal control regions. Analysis of data from 336 control peaks from pancreatic tumor cells (Dhara et al., Pancreatic

cancer prognosis is predicted by an ATAC-array technology for assessing chromatin accessibility. *Nat Commun* **12**, 3044 (2021).) and 232 control peaks from and CD8+ T cells (Shin, H.M., Kim, G., Kim, S. *et al.* Chromatin accessibility of circulating CD8+ T cells predicts treatment response to PD-1 blockade in patients with gastric cancer. *Nat Commun* **12**, 975 (2021)) identified 4 peaks that were present in both datasets. While designing qPCR array, these 4 constantly accessible genomic locations were taken as internal control targets to identify differentially accessible regions between pancreatic cancer patient samples of different prognostic outcomes.

8.6 EXAMPLE 6 – Designing ATAC-qPCR array primers

[00309] This example illustrates methods for designing ATAC-qPCR array primers for testing the ACRs identified in Example 5.

[00310] The median length of the accessible chromatin regions (ACRs) is 628 bp as shown in Table 3, ranging from minimum of 293, and maximum of 1023. We selected the middle regions (closest to the summit) of all these ACRs, where the odds of representation of these ACRs by the primer oligos are the maximum. The primers were designed by Primer Express™ Software v3.0.1 (cat#4363991). Table 4 shows exemplary primer sequences.

Table 4. ATAC-qPCR array primer sequences							
Target Gene Regulatory Region	Target Coordinates	Forward Primer (5'-3')	SEQ ID NO.	Reverse Primer (5'-3')	SEQ ID NO.	Melting Temperature °C	Amplicon length
ARHGEF10	chr8:1878704-1879351	TGGAGTAAG CACAGGAGC CGCT	SEQ ID NO.: 1	TGAGAGGGA GGCAACCAG AGGC	SEQ ID NO.: 16	87.78	114
CLDN23	chr8:8547367-8547711	TCCAGCCCA CCTCCTCCC AATG	SEQ ID NO.: 2	TGCTTGTTG CCAACTCTGC TC	SEQ ID NO.: 17	81.13	112
SPATA4	chr4:177114274-177114599	TGCTCAGTTT CATAGGTGA CTCA	SEQ ID NO.: 3	AGTGTGCCAT GCTAATTTCC TGGA	SEQ ID NO.: 18	78.93	139
ITGAV	chr2:187426114-187426881	TTACCACAG CCC'TTGGGC GAGA	SEQ ID NO.: 4	TGGAGTCGGG GGAGGGGTA ACA	SEQ ID NO.: 19	84.6	112
FIG4	chr6:110064994-110065287	ACGCTCTGG GAAGCCTCT TCCT	SEQ ID NO.: 5	AGACACAGTG AGCTGTCCCA GC	SEQ ID NO.: 20	81.64	110
MAP2K2	chr19:4084177-4084702	GGCCGCTGC TGGTTTCGTT TTG	SEQ ID NO.: 6	GGGCTCCAGG GCAGGTTAAG GA	SEQ ID NO.: 21	85.83	130

Table 4. ATAC-qPCR array primer sequences							
Target Gene Regulatory Region	Target Coordinates	Forward Primer (5'-3')	SEQ ID NO.	Reverse Primer (5'-3')	SEQ ID NO.	Melting Temperature °C	Amplicon length
PPAP2B	chr1:56933904-56934476	GGCTTCACT GGTGACCAA GACAGC	SEQ ID NO.: 7	AGCTGACGGG AGAGGCTTTC GT	SEQ ID NO.: 22	80.87	114
TTC19	chr17:15917197-15917706	GCAGTTCAG CAATAGGGA GCAGGC	SEQ ID NO.: 8	TCAACCACCA GGGGAGCAT GGG	SEQ ID NO.: 23	80.31	132
RN7SL30P	chr3:152974102-152975125	CTCTGTGTGCC CAGGCTGGA GTG	SEQ ID NO.: 9	GGCCCTTTGT CGAAACGTTT GCA	SEQ ID NO.: 24	80.72	102
PAPL	chr19:39569172-39569875	TTTGGGAGG CTGAGGTGG GAGG	SEQ ID NO.: 10	TGTCACCCAG GCTGGAGTGC AT	SEQ ID NO.: 25	74.43	101
CNBP	chr3:128914473-128915151	ACCAGCCCT CGGAACTG CTGA	SEQ ID NO.: 11	GCATGCTCTG TGGCTGGCTG AA	SEQ ID NO.: 26	81.33	120
RP11	chr1:226270679-226271550	TCCCCAGCA TCTCTCCAG CGTC	SEQ ID NO.: 12	TTCTCTCTGG CACCTGGGGC TG	SEQ ID NO.: 27	88.4	138
XRCC2	chr7:152372887-152373496	TCACCTCGG TCCCAGACT CAGC	SEQ ID NO.: 13	GCGCAGTTGG TGAATGGCGT TG	SEQ ID NO.: 28	86.27	109
C1orf131	chr1:231376653-231377603	CAGCCGCAC CATGGAGTC TTCC	SEQ ID NO.: 14	GGGTACTATT TCGCGCGGCT CC	SEQ ID NO.: 29	87.54	140
GTF3C6	chr6:111279570-111280284	CTGGCAGAA GCAATTTGC GCGG	SEQ ID NO.: 15	GCCTTCTAGT CACTGGCCAC GC	SEQ ID NO.: 30	89.01	125

[00311] The first 3 primers (ARGFEF10, CLDN23, and SPATA4) were specific to three chromatin *cis*-regulatory regions that are differentially accessible to good prognosis patients (“blue” regions), the next set of 8 primers (MAPK2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL, and ITGAV) were specific to 8 chromatin *cis*-regulatory regions that are differentially accessible to poor prognosis patients (“red” regions), and the remaining 4 primers (GTF3C6, C1orf131, XRCC2, and RP11) were specific to 4 chromatin *cis*-regulatory regions that are constitutively accessible to all patients (“green” regions).

[00312] All these custom-designed oligonucleotides sequences (primer pairs as displayed in Table 2) were first tested for specificity in silico by NCBI Basic Local Alignment Tool (BLAST), and then the oligonucleotides were purchased from IDT (Integrated DNA Technologies, Coralville, IA).

[00313] FIGs. 7A and 7B provide results from melting curve analysis showing a single peak for each primer set. Quantitative measurement of target accessible region relative to control regions were performed in triplicates using Power SYBR Green PCR Master Mix (Applied Biosystems, Warrington, UK cat # 4368706) following the manufacturer's recommendations. All the qPCR experiments were run on QuantStudio™ 3 Real-Time PCR System, 96-well, 0.2 mL (Applied Biosystem cat# A28567). Commercially available male genomic DNA (Agilent Technologies cat#5190-4370) were used as the template to test the performances of all the primer sets. The single products were tested by Melting curve analysis as shown in FIGs. 7A and 7B, each amplicon showed only one peak at specific temperature (as listed in Table 4) confirming single product per primer set. The specificity of the primer sets was confirmed by Sanger sequencing analysis of the amplicons.

8.7 EXAMPLE 7 – Determining a prognostic score of a patient using ATAC-qPCR array primers

[00314] This example provides a method for determining prognostic score of a patient using ATAC-qPCR array primers described in Example 6.

[00315] We selected 14 patients with pancreatic cancer who had undergone upfront surgery followed by Gemcitabine/ Nab-Paclitaxel adjuvant chemotherapy. These patients were monitored for a median follow up time of 4.15 years post-surgery. Seven (7) patients showed good prognosis with a median disease-free survival (DFS) of 1478 days (ranging from 1234 to 1645), and the other 7 patients showed poor prognosis with a median DFS of 47 days (ranging from 36 to 207) with the similar treatment regimen. FIG. 8 shows the Kaplan-Meier graph showing patient with good prognosis and poor prognosis. We first estimated the relative accessibility of the differentially accessible chromatin regions (the blue, and red regions, normalized with the 4 green regions) by 2^{-dCt} method in each patient by qPCR analyses of the individual ATAC-libraries prepared from them. The dCt values for each target region was calculated as below:

$dCt = Ct \text{ values of the differential (blue or red) regions} - \text{Geometric mean } Ct \text{ values of the control (green) regions}$

[00316] FIGs. 9A and 9B show the results of ATAC-qPCR analysis of the 11 target regions using the 4 control regions for normalization. The relative quantitation of blue and red regions in each

individual patient were shown by bar plot, where the blue bars represented the blue target regions and the red bars represented the red target regions.

[00317] Next, we calculated the Prognostic scores using the ATAC-qPCR analytical methods as displayed below:

Prognostic score (PS) by ATAC-qPCR array = 2^{-dCt} of blue regions - 2^{-dCt} of red regions

[00318] Using the formula described above we calculated the individualized PS for each patient and analyzed the PS of good and poor prognosis groups. The box plot as displayed in **FIG. 10** demonstrated a statistically significant difference (t test $p=0.034$) of PS between the 7 good and 7 poor prognosis patients.

[00319] The data demonstrate that a set of targeting oligonucleotide probes required for effectively determining a reliable prognostic score can be less than 100, or as few as 12 probes. The set of targeting oligonucleotide probes required for effectively determining good prognosis can be as few as 3 probes, and the set of targeting oligonucleotide probes required for effectively determining poor prognosis can be as few as 8 probes. The result demonstrate that ATAC-qPCR array is a robust, reliable and cost-effective method for determining prognostic score of a patient having, or at risk of developing pancreatic cancer. Such information is critical for the selection of treatment modalities, which can enhance the subject's likelihood of disease-free survival.

9. EMBODIMENTS

[00320] Embodiment 1. A method for determining an epigenetic landscape associated with a specific phenotypic trait of a biological sample, the method comprising:

providing a biological sample comprising morphologically intact nuclei or intact nucleosome (histone-DNA) structure;

contacting the intact nuclei or intact nucleosome to a transposase complex to produce a population of tagged DNA fragments representing accessible chromatin regions (ACRs) of the intact nuclei or intact nucleosome (histone-DNA) structure;

hybridizing a set of targeting oligonucleotide probes to a specific region on the ACRs to generate targeted ACR fragments, wherein the targeting oligonucleotide probes specifically targets no more than 100 differentially accessible chromatin regions selected from Table 1 or Table 2, wherein the targeting oligonucleotide probes comprise:

a first subset of oligonucleotide probes targeting ACRs associated with a first phenotype, and

a second subset of oligonucleotide probes targeting ACRs associated with a second phenotype;

amplifying the targeted ACR fragments associated with the first phenotype and the second phenotype obtained in (c); and

quantifying the amount of amplified targeted ACR fragments, thereby determining the epigenetic landscape associated with the first and the second phenotypic traits of the biological sample.

[00321] Embodiment 2. The method of embodiment 1, wherein the amplification fragment comprises a mean size of less than 100 bp.

[00322] Embodiment 3. The method of embodiment 1 or embodiment 2, wherein the first phenotype is recurrence of a cancer within one year of surgical resection and the second phenotype is non-recurrence of a cancer within one year of surgical resection.

[00323] Embodiment 4. The method of embodiment 1 or embodiment 2, wherein the first phenotype is non-responder and the second phenotype is responder to a cancer therapy.

[00324] Embodiment 5. The method of embodiment 4, wherein the cancer therapy is selected from chemotherapy, immunotherapy, and radiation.

[00325] Embodiment 6. The method of any one of embodiments 1-5, further comprising assessing nuclear localization of one or more biomarkers capable of modulating gene expression through complementary binding to one or more specific regions on the amplified targeted ACR fragments.

[00326] Embodiment 7. The method of embodiment 6, wherein the biomarker is a transcription factor.

[00327] Embodiment 8. The method of embodiment 7, wherein the transcription factor is selected from ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5,

HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFX3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.

[00328] Embodiment 9. The method of any one of embodiments 1-8, wherein the biological sample is selected from a tumor biopsy, surgically resected tumor specimen, or liquid biopsy.

[00329] Embodiment 10. The method of any one of embodiments 1-8, wherein the biological sample is pancreatic ductal adenocarcinoma tissue.

[00330] Embodiment 11. The method of embodiment 9 or embodiment 10, wherein the biological sample comprises circulating shedding tumor cells or circulating tumor DNA (ctDNA).

[00331] Embodiment 12. The method of embodiment 9 or embodiment 10, wherein the biological sample comprises treatment-naïve malignant cells.

[00332] Embodiment 13. The method of embodiment 9 or embodiment 10, wherein the biological sample is collected from a patient who had been treated with one or more treatment modalities.

[00333] Embodiment 14. The method of any one of embodiments 1-13, wherein the phenotypic trait is responsiveness to a treatment modality.

[00334] Embodiment 15. The method of embodiment 13 or embodiment 14, wherein the treatment modality is selected from the group consisting of surgical resection, chemotherapy, radiation, immunotherapy, and a combination thereof.

[00335] Embodiment 16. The method of any one of embodiments 1-15, further comprising isolating nucleosomal DNA from the cell nuclei of the biological sample.

[00336] Embodiment 17. The method of embodiment 16, wherein the nuclei are isolated and in a manner that maintains nucleosome structure.

[00337] Embodiment 18. The method of any one of embodiments 1-17, wherein the method does not include sequencing the tagged fragments or amplicons thereof.

10. EQUIVALENTS AND INCORPORATION BY REFERENCE

[00338] While the invention has been particularly shown and described with reference to a preferred embodiment and various alternate embodiments, it will be understood by persons skilled in

the relevant art that various changes in form and details can be made therein without departing from the spirit and scope of the invention.

[00339] All references, issued patents and patent applications cited within the body of the instant specification are hereby incorporated by reference in their entirety, for all purposes. In particular, PCT International Patent Application No: PCT/US2019/046301, U.S. Patent Application No.: 17/268,195, U.S. Patent Application No: 17/324,093, and Dhara et al., Pancreatic cancer prognosis is predicted by an ATAC-array technology for assessing chromatin accessibility. Nat Commun **12**, 3044 (2021), are each hereby incorporated by reference in their entireties.

WHAT IS CLAIMED:

1. A method for determining a prognostic score indicative of a subject's responsiveness to one or more treatment modalities or indicative of a duration of disease-free survival, the method comprising:

- (a) contacting a biological sample obtained from the subject with a transposase complex to produce a population of tagged DNA fragments representing accessible chromatin regions of intact nuclei or intact nucleosome structure, wherein the biological sample comprises pancreatic ductal adenocarcinoma cells having morphologically intact nuclei or intact nucleosomes;
- (b) hybridizing a set of targeting oligonucleotide probes to a specific region on the accessible chromatin regions to generate targeted accessible chromatin region fragments, wherein the targeting oligonucleotide probes specifically target differentially accessible chromatin regions, and wherein the targeting oligonucleotide probes comprise:
 - (iii) a first subset of oligonucleotide probes targeting accessible chromatin regions associated with a first phenotype, and
 - (iv) a second subset of oligonucleotide probes targeting accessible chromatin regions associated with a second phenotype;
- (c) amplifying the targeted accessible chromatin region fragments obtained in (b) that are associated with the first phenotype and the second phenotype; and
- (d) determining a prognostic score based on epigenetic signature values of the biological sample,
 - wherein the prognostic score is determined based on a differential of a first epigenetic signature value and a second epigenetic signature value, and
 - wherein the prognostic score is indicative of the subject's responsiveness to the one or more treatment modalities or indicative of a duration of disease-free survival.

2. The method of claim 1, further comprising, prior to step (a), enriching the biological sample for tumor cells.

3. The method of claim 1 or claim 2, further comprising contacting the biological sample with an agent to isolate tumor cells from non-tumor cells in the biological sample to enrich the sample for tumor cells.

4. The method of claim 3, wherein the agent comprises antibody-conjugated magnetic beads, EpCAM-conjugated magnetic beads, or a combination thereof.
5. The method of any one of claims 1-4, further comprising:
 - (i) attaching a detectable label to the tagged DNA fragments to produce labeled fragments; and
 - (ii) contacting the detectable labeled fragments to the set of targeting oligonucleotide probes.
6. The method of any one of claims 1-5, further comprising quantifying the amount of amplified targeted accessible chromatin region fragments to obtain the first epigenetic signature value and the second epigenetic value.
7. The method of any one of claims 1-6, wherein the set of targeting oligonucleotide probes are selected from any pair of oligonucleotide probes in Table 4.
8. The method of any one of claims 1-7, wherein the targeting oligonucleotide probes comprises a nucleic acid sequence having a sequence of any one of SEQ ID NOs.: 1-30.
9. The method of any one of claims 1-8, wherein the set of targeting oligonucleotide probes comprises at least one set of probes targeting ARHGEF10, CLDN23, C12orf36, and SPATA4.
10. The method of any one of claims 1-8, wherein the set of targeting oligonucleotide probes comprises at least one set of probes targeting MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, and ITGAV.
11. The method of any one of claims 1-10, wherein the set of targeting oligonucleotide probes comprises at least one set of probes targeting GTF3C6, LINC01703, C1orf131, and XRCC2.
12. The method of any one of claims 1-11, wherein the accessible chromatin regions are selected from any one of the accessible chromatin regions in FIG. 9A, FIG. 9B, and/or Table 3.
13. The method of claim 12, wherein the accessible chromatin regions are selected from any one of the accessible chromatin regions in Table 3.
14. The method of any one of claims 1-13, further comprising the step of comparing the first epigenetic signature value to the second epigenetic signature value to obtain a differential value.
15. The method of any one of claims 1-14, further comprising normalizing the differential value with at least one of a positive control value and one of a negative control value to obtain the prognostic score.

16. The method of claim 15, wherein the prognostic score is at least 0.6.
17. The method of claim 16, further comprising detecting nuclear localization of at least one of a transcription factor selected from any one of the transcription factors in Tables 2A and 2B.
18. The method of claim 17, wherein the transcription factors are selected from ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFH3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.
19. The method of claim 18, wherein the transcription factors are selected from ZKSCAN1A, HNF1B, or a combination thereof.
20. The method of any one of claims 1-19, further comprising predicting a long duration of disease-free survival when the first epigenetic signature value is significantly higher than the second epigenetic signature value and/or predicting a short duration of disease-free survival when the second epigenetic signature value is significantly higher than the first epigenetic value.
21. The method of any one of claims 1-20, wherein the first phenotype is recurrence of a cancer within one year of surgical resection and the second phenotype is non-recurrence of a cancer within one year of surgical resection.
22. The method of any one of claims 1-20, wherein the first phenotype is non-responder and the second phenotype is responder to a cancer therapy.
23. The method of claim 22, wherein the cancer therapy is selected from chemotherapy, immunotherapy, radiation, or combinations thereof.
24. The method of any one of claims 1-20, wherein the second phenotype is having a median disease-free survival of between 50 to 1500 days.
25. The method of any one of claims 1-20, wherein the second phenotype is having a median disease-free survival of at least 350 days.
26. The method of any one of claims 1-20, wherein the first phenotype is having a median disease-free survival of between 1 to 350 days.
27. The method of any one of claims 1-20, wherein the first phenotype is having a median disease-free survival of less than 50 days.

28. The method of any one of claims 1-27, wherein the biological sample comprises treatment-naïve malignant cells.
29. The method of claim 28, wherein the subject is a treatment naïve patient who has not received the one or more treatment modalities.
30. The method of any one of claims 1-27, wherein the subject is under treatment or has been treated with the one or more treatment modalities.
31. The method of any one of claims 1-30, wherein the one or more treatment modalities are selected from resecting cancerous tissue, neo-adjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, an epigenetic drug, or combinations thereof.
32. The method of claim 31, wherein the epigenetic drug is selected from DNMT inhibitor, an HDAC inhibitor, an EZH2 inhibitor, or combinations thereof.
33. The method of claim 32, wherein the neo-adjuvant chemotherapy and/or adjuvant chemotherapy is selected from gemcitabine, nab-paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, leucovorin, capecitabine, cisplatin, or combinations thereof.
34. The method of any one of claims 1-33, wherein the biological sample is selected from a tumor biopsy or surgically resected tumor specimen.
35. The method of any one of claims 1-34, wherein the method does not include sequencing the tagged fragments or amplicons thereof.
36. The method of any one of claims 1-35, wherein the amplified targeted accessible chromatin fragments comprise a mean size of about 120 bp.
37. A method of treating a subject having, or suspected of having, pancreatic ductal adenocarcinoma with one or more treatment modalities, the method comprising:
- (a) receiving a prognostic score indicative of the subject's responsiveness to one or more treatment modalities or indicative of a duration of disease-free survival,
wherein the prognostic score is determined based on epigenetic signature values of a biological sample from the subject that comprises pancreatic ductal adenocarcinoma cells having morphologically intact nuclei or intact nucleosomes, the biological sample having been contacted with a transposase complex to produce a population of tagged DNA fragments representing accessible chromatin regions of the intact nuclei or intact nucleosome structure,

wherein a set of targeting oligonucleotide probes were hybridized to a specific region on the accessible chromatin regions to generate targeted accessible chromatin region fragments,

wherein the targeting oligonucleotide probes specifically target differentially accessible chromatin regions,

wherein the prognostic score is determined based on a differential of a first epigenetic signature value and a second epigenetic signature value; and

(b) treating the subject with the one or more treatment modalities based on the prognostic score.

38. The method of claim 37, wherein the biological sample is, prior to step (a), enriched for tumor cells.

39. The method of claim 37 or 38, wherein the enriched tumor cells are obtained by contacting the biological sample with an agent to isolate tumor cells from non-tumor cells in the biological sample to enrich the sample for tumor cells.

40. The method of claim 39, wherein the agent comprises antibody-conjugated magnetic beads, EpCAM-conjugated magnetic beads, or a combination thereof.

41. The method of any one of claims 37-40, wherein the biological sample is obtained by:

- (i) attaching a detectable label to the tagged DNA fragments to produce labeled fragments; and
- (ii) contacting the detectable labeled fragments to the set of targeting oligonucleotide probes.

42. The method of any one of claims 37-41, wherein the first epigenetic signature value and the second epigenetic signature value are obtained by quantifying the amount of amplified targeted accessible chromatin region fragments.

43. The method of any one of claims 37-42, wherein the set of targeting oligonucleotide probes are selected from any pair of oligonucleotide probes in Table 4.

44. The method of any one of claims 37-43, wherein the targeting oligonucleotide probes comprises a nucleic acid sequence having a sequence of any one of SEQ ID NOs.: 1-30.

45. The method of any one of claims 37-44, wherein the set of targeting oligonucleotide probes comprises at least one set of probes targeting ARHGEF10, CLDN23, C12orf36, and SPATA4.

46. The method of any one set of probes targeting claims 37-45, wherein the set of targeting oligonucleotide probes comprises probes targeting at least one of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, and ITGAV.
47. The method of any one of claims 37-46, wherein the set of targeting oligonucleotide probes comprises at least one set of probes targeting GTF3C6, LINC01703, C1orf131, and XRCC2.
48. The method of any one of claims 37-47, wherein the accessible chromatin regions are selected from any one of the accessible chromatin regions in FIG. 9A, FIG. 9B, and/or Table 3.
49. The method of claim 48, wherein the accessible chromatin regions are selected from any one of the accessible chromatin regions in Table 3.
50. The method of any one of claims 37-49, wherein determining the prognostic score comprises the step of comparing the first epigenetic signature value to the second epigenetic signature value to obtain a differential value.
51. The method of any one of claims 37-50, wherein determining the prognostic score comprises the step of normalizing the differential value with at least one of a positive control value and a negative control value to obtain the prognostic score.
52. The method of claim 51, wherein the prognostic score is at least 0.6.
53. The method of claim 52, wherein determining the prognostic score comprises the step of comprises detecting nuclear localization of a transcription factor selected from any one of transcription factors in Tables 2A and 2B.
54. The method of claim 53, wherein the transcription factors are selected from ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFH3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.
55. The method of claim 54, wherein the transcription factors are selected from ZKSCAN1A, HNF1B, or a combination thereof.
56. The method of any one of claims 37-55, wherein determining the prognostic score comprises the step of predicting a long duration of disease-free survival when the second

epigenetic signature value is significantly higher than the first epigenetic signature value and/or predicting a short duration of disease-free survival when the first epigenetic signature value is significantly higher than the first epigenetic value.

57. The method of any one of claims 37-56, wherein the first phenotype is recurrence of a cancer within one year of surgical resection and the second phenotype is non-recurrence of a cancer within one year of surgical resection.

58. The method of any one of claims 37-57, wherein the second phenotype is responder and the first phenotype is non-responder to a cancer therapy.

59. The method of claim 58, wherein the cancer therapy is selected from chemotherapy, immunotherapy, radiation, or combinations thereof.

60. The method of any one of claims 37-57, wherein the second phenotype is having a median disease-free survival of between 50 to 1500 days.

61. The method of any one of claims 37-57, wherein the second phenotype is having a median disease-free survival of at least 350 days.

62. The method of any one of claims 37-57, wherein the first phenotype is having a median disease-free survival of between 1 to 350 days.

63. The method of any one of claims 37-57, wherein the first phenotype is having a median disease-free survival of less than 50 days.

64. The method of any one of claims 37-63, wherein the biological sample comprises treatment-naïve malignant cells.

65. The method of claim 64, wherein the subject is a treatment naïve patient who has not received the one or more treatment modalities.

66. The method of any one of claims 37-65, wherein the subject is under treatment or has been treated with the one or more treatment modalities.

67. The method of any one of claims 37-66, wherein the one or more treatment modalities are selected from resecting cancerous tissue, neo-adjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, an epigenetic drug, or combinations thereof.

68. The method of claim 67, wherein the epigenetic drug is selected from DNMT inhibitor, an HDAC inhibitor, an EZH2 inhibitor, or combinations thereof.

69. The method of claim 68, wherein the neo-adjuvant chemotherapy and/or adjuvant chemotherapy is selected from gemcitabine, nab-paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, leucovorin, capecitabine, cisplatin, or combinations thereof.
70. The method of any one of claims 37-69, wherein the biological sample is selected from a tumor biopsy or surgically resected tumor specimen.
71. The method of any one of claims 37-70, wherein obtaining the targeted accessible chromatin region fragments does not include the step of sequencing the tagged fragments or amplicons thereof.
72. The method of any one of claims 37-71, wherein determining the prognostic score comprises the step of amplifying accessible chromatin fragment having a mean size of about 120 bp.
73. The method of any one of claims 1-72, wherein the set of targeting oligonucleotide probes required for effectively determining the prognostic score is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.
74. The method of claim 73, wherein the set of targeting oligonucleotide probes required for effectively determining the prognostic score is about 12.
75. The method of claim 74, wherein the set of targeting oligonucleotide probes required for effectively determining good prognosis or poor prognosis is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.
76. The method of claim 75, wherein the set of targeting oligonucleotide probes required for effectively determining good prognosis is about 3.
77. The method of claim 76, wherein the set of targeting oligonucleotide probes required for effectively determining poor prognosis is about 8.
78. A kit for determining an epigenetic landscape associated with a specific phenotypic trait of a biological sample, the kit comprising:
- (a) an array configured to detect targeted accessible chromatin region fragments obtained from the biological sample, wherein the array comprises a panel of sets of targeting oligonucleotide probes specifically targeting differentially accessible chromatin regions;
 - (b) reagents; and

- (c) instructions for amplifying and quantifying the targeted accessible chromatin region fragments to obtain a first epigenetic signature value and a second epigenetic value.
79. The kit of claim 78, wherein the panel of targeting oligonucleotide probes is arranged as described in FIG. 4A or 4B.
80. A kit for determining an epigenetic landscape associated with a specific phenotypic trait of a biological sample, the kit comprising:
- (a) one or more sets of targeting oligonucleotide probes for detect targeted accessible chromatin region fragments obtained from the biological sample, wherein the targeting oligonucleotide probes specifically target and amplify differentially accessible chromatin regions to generate one or more targeted accessible chromatin region fragments;
 - (b) reagents; and
 - (c) instructions for amplifying and quantifying the targeted accessible chromatin region fragments to obtain a first epigenetic signature value and a second epigenetic value.
81. The kit of any one of claims 78-80, wherein the biological sample comprises pancreatic ductal adenocarcinoma cells having morphologically intact nuclei or intact nucleosome (histone-DNA) structure.
82. The kit of any one of claims 78-81, further comprising reagents and instruction for obtaining the biological sample by contacting the morphologically intact nuclei or intact nucleosome (histone-DNA) structure to a transposase complex to produce a population of tagged DNA fragments representing the targeted accessible chromatin region fragments.
83. The kit of any one of claims 78-82, wherein the targeting oligonucleotide probes comprises a nucleic acid sequence having a sequence of any one of SEQ ID NOs.: 1-30.
84. The kit of any one of claims 78-83, wherein the set of targeting oligonucleotide probes comprises probes targeting at least one of ARHGEF10, CLDN23, C12orf36, and SPATA4.
85. The kit of any one of claims 78-83, wherein the set of targeting oligonucleotide probes comprises probes targeting at least one of MAP2K2, PPAP2B, CNBP, FIG4, TTC19, PAPL, RN7SL300P, and ITGAV.
86. The kit of any one of claims 78-85, wherein the set of targeting oligonucleotide probes comprises probes targeting at least one of GTF3C6, LINC01703, C1orf131, and XRCC2.

87. The kit of claim any one of claims 78-86, further comprising reagents and instructions for enriching the biological sample obtained from the subject for tumor cells.
88. The kit of claim 87, wherein the reagents comprise antibody-conjugated magnetic beads, EpCAM-conjugated magnetic beads, or a combination thereof to isolate tumor cells from non-tumor cells in the biological sample.
89. The kit of any one of claims 78-88, further comprising reagents and instructions for:
- (i) attaching a detectable label to the tagged DNA fragments to produce labeled fragments; and
 - (ii) contacting the detectable labeled fragments to the set of oligonucleotide probes.
90. The kit of any one of claims 78-89, further comprising instructions for determining a prognostic score indicative of the subject's responsiveness to one or more treatment modalities based on a differential score of the first epigenetic signature value and the second epigenetic value.
91. The kit of any one of claims 78-90, wherein the instruction comprises normalizing the differential value with at least one of a positive control value and a negative control value to obtain the prognostic score.
92. The kit of claim 91, wherein the prognostic score is at least 0.6.
93. The kit of any one of claims 78-92, further comprising reagents and instructions for detecting nuclear localization of a transcription factor selected from any one of transcription factors in Tables 2A and 2B.
94. The kit of claim 93, wherein the transcription factors are selected from ZKSCAN1, EPAS1, RUNX2, ZNF410, MAFF, RREB1, NR3C2, SMAD1, RUNX1, ZNF32, ZSCAN4, HOXB1, POU3F1, ZBTB3, CLOCK, TCF15, GCM1, HINFP, CGBP, MYPOP, ZNF384, GMEB2, E2F5, AC012531.1, ZBTB7B, HOXC9, HNF4G, CREB1, ATF2, E2F2, SP3, ARID5A, ZFP161, OTP, PBX3, ZBTB33, ONECUT3, ONECUT3, DLX2, HNF4A, PRRX1, TCFL5, HOXB7, IRF6, GRHL1, FOXD2, ISL1, MLL, GATA2, GATA1, HMBOX1, NRF1, ZFH3, ONECUT1, TET1, E2F3, DNMT1, CTCFL, CTCF, HNF1B, and HNF1A.
95. The kit of claim 94, wherein the transcription factors are selected ZKSCAN1A, HNF1B, or a combination thereof.
96. The kit of any one of claims 78-95, further comprising reagents and instructions for predicting a long duration of disease-free survival when the second epigenetic signature value is

significantly higher than the first epigenetic signature value and/or predicting a short duration of disease-free survival when the first epigenetic signature value is significantly higher than the second epigenetic value.

97. The kit of any one of claims 78-96, further comprising reagents and instructions for determining a first phenotype and second phenotype of the subject's responsiveness to one or more treatment modalities.

98. The kit of claim 97, wherein the first phenotype is recurrence of a cancer within one year of surgical resection and the second phenotype is non-recurrence of a cancer within one year of surgical resection.

99. The kit of claim 97, wherein the first phenotype is non-responder and the second phenotype is responder to a cancer therapy.

100. The kit of claim 99, wherein the cancer therapy is selected from chemotherapy, immunotherapy, radiation, or combinations thereof.

101. The kit of any one of claims 78-100, wherein the second phenotype is having a median disease-free survival of between 50 to 1500 days.

102. The kit of any one of claims 78-100, wherein the second phenotype is having a median disease-free survival of at least 350 days.

103. The kit of any one of claims 78-100, wherein the first phenotype is having a median disease-free survival of between 1 to 350 days.

104. The kit of any one of claims 78-100, wherein the first phenotype is having a median disease-free survival of less than 50 days.

105. The kit of any one of claims 78-104, wherein the biological sample comprises treatment-naïve malignant cells.

106. The kit of claim 105, wherein the subject is a treatment naïve patient who has not received the one or more treatment modalities.

107. The kit of any one of claim 78-106, wherein the subject is under treatment or has been treated with the one or more treatment modalities.

108. The kit of any one of claims 78-107, wherein the one or more treatment modalities are selected from resecting cancerous tissue, neo-adjuvant chemotherapy, adjuvant chemotherapy, immunotherapy, an epigenetic drug, or combinations thereof.

109. The kit of claim 108, wherein the epigenetic drug is selected from DNMT inhibitor, an HDAC inhibitor, an EZH2 inhibitor, or combinations thereof.
110. The kit of claim 109, wherein the neo-adjuvant chemotherapy and/or adjuvant chemotherapy is selected from gemcitabine, nab-paclitaxel, fluorouracil (5-FU), irinotecan, oxaliplatin, leucovorin, capecitabine, cisplatin, or combinations thereof.
111. The kit of any one of claims 78-110, wherein the biological sample is selected from a tumor biopsy or surgically resected tumor specimen.
112. The kit of any one of claims 78-111, wherein obtaining the targeted accessible chromatin region fragments does not include sequencing the tagged fragments or amplicons thereof.
113. The kit of any one of claims 78-112, wherein the amplified targeted accessible chromatin fragments comprise a mean size of about 120 bp.
114. The kit of any one of claims 78-113, wherein the set of targeting oligonucleotide probes required for effectively determining the prognostic score is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.
115. The kit of claim 114, wherein the set of targeting oligonucleotide probes required for effectively determining the prognostic score is about 12.
116. The kit of claim 115, wherein the set of targeting oligonucleotide probes required for effectively determining good prognosis or poor prognosis is less than 100, 90, 80, 70, 60, 50, 40, 30, 20, or 10.
117. The kit of claim 116, wherein the set of targeting oligonucleotide probes required for effectively determining good prognosis is about 3.
118. The kit of claim 116, wherein the set of targeting oligonucleotide probes required for effectively determining poor prognosis is about 8.