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OpenGDC file format definition

Contents

Introduction

The Cancer Genome Atlas (TCGA) is one of the most relevant collections of open data from 33 different tumor types and more than 1000 involved healthy and diseased patients. It includes data regarding different types of experiments including Copy Number Variations, DNA-sequencing, DNA-Methylation, miRNA-sequencing and RNA-sequencing. TCGA data have recently been updated, both in the contents and in the structure. The new portal hosting TCGA datasets, along with other cancer-focused projects' data, is called Genomic Data Commons (GDC).

OpenGDC is a novel software implementing an original approach for the automatic extraction, extension and conversion of the public experiment data of the TCGA projects available in GDC; available at http://www.bioinformatics.deib.polimi.it/opengdc/, it can provide such data converted in BED, CSV, GTF, JSON and XML formats, to make them as much usable as possible for all domain experts. Additionally, it is also a new public FTP repository with original open TCGA data sets and their BED format converted version, created and made accessible through the following address: ftp://geco.deib.polimi.it/opengdc/. Other specific goals of OpenGDC are: (i) automate the extraction of public TCGA data and metadata from the GDC repository and the proprietary tab-delimited format in which they are provide by GDC; (ii) extend them by integrating information retrieved from different public sources such as NCBI Genome and Gene databases, HGNC, UCSC and MIRBase; (iii) convert them into the BED format, which is more usable for biologists, bioinformaticians and life scientists, and additionally it is fully supported by the GenoMetric Query Language (GMQL)[1]. Based on the Genomic Data Model (GDM)[2], GMQL is implemented in an innovative system[3] able to process numerous and heterogeneous genomic data in the cloud in order to extract information about their metric (co)occurrences genome-wide (http://www.bioinformatics.deib.polimi.it/GMQLsystem/).

We had previously proposed TCGA2BED[4], from which OpenGDC is inspired. TCGA2BED provided a Java software application for the automatic extraction, extension and conversion of genomic and clinical data of cancer retrieved from the old TCGA portal. TCGA2BED is also an FTP repository, available at ftp://bioinf.iasi.cnr.it/, containing the original public data from TCGA and the same data converted in BED format and extended with additional information, for a total of more than 650 GB. Additionally, the TCGA2BED software is accessible under GPL license and it is freely

[1] *Masseroli M, Pinoli P, Venco F, Kaitoua A, Jalili V, Paluzzi F, Muller H, Ceri S*: **GenoMetric Query Language: A novel approach to large-scale genomic data management**. *Bioinformatics* 2015; 31(12):1881-1888.

[2] *Masseroli M, Kaitoua A, Pinoli P, Ceri S.* **Modeling and interoperability of heterogeneous genomic big data for integrative processing and querying**. *Methods* 2016; 111: 3-11.

[3] *Masseroli M, Canakoglu A, Pinoli P, Kaitoua A, Gulino A, Horlova O, Nanni L, Bernasconi A, Perna S, Stamoulakatou E, Ceri S.* **Processing of big heterogeneous genomic datasets for tertiary analysis of Next Generation Sequencing data**. *Bioinformatics* 2019; 35(5):729-736.

[4] *Cumbo F, Fiscon G, Ceri S, Masseroli M, Weitschek E.* ***TCGA2BED: extracting, extending, integrating, and querying The Cancer Genome Atlas.*** *BMC Bioinformatics, 2017; 18(1), 6.*

available from the project page at http://bioinf.iasi.cnr.it/tcga2bed/. However, in July 2016 TCGA closed its data portal, making its data unavailable. Later, the U.S. National Cancer Institute (NCI), through the same authors of the TCGA project, opened the new GDC portal that currently hosts most data from TCGA (not all previously available datasets are available in GDC, e.g., isoform expression and splicing ones) and other cancer research programs.

Unfortunately, TCGA2BED software can no longer be used, nor the TCGA2BED repository updated, because of the major changes during the data portal shift. This motivated our implementation of OpenGDC, which solves the issues arisen in the transition from the TCGA data portal to the GDC one. Unlike TCGA2BED, beside extending TCGA genomic data and standardize the format in which they are provided by GDC, in OpenGDC we also integrate, normalize and make non-redundant their multiple metadata available with different representations; we do so by mapping them to a unique data model and widely exploiting the GDC APIs to interact with and extract the GDC data.

Input data sets

For the conversion of GDC TCGA data files into the BED format, we actually take into account the following data sets, which include all the genomic data that the Genomic Data Commons (GDC) is currently providing publicly:

- Masked Somatic Mutation (msm)
- Gene Expression Quantification (geq)
- Methylation Beta Value (mbv)
- Copy Number Segment (cns)
- Masked Copy Number Segment (mcns)
- miRNA Expression Quantification (meq)
- Isoform Expression Quantification (ieq)
- Meta data: Biospecimen Supplement
- Meta data: Clinical Supplement

All data are retrieved from the "*GDC Application Programming Interface (API)*", available at https://gdc.cancer.gov/developers/gdc-application-programming-interface-api.

Following abbreviations are used for referring to the experimental data sets

Experiment	**Abbreviation**	**Access**
Copy Number Segment	cns	Open
Gene Expression Quantification	geq	Open
Isoform Expression Quantification	ieq	Open
Masked Copy Number Segment	mcns	Open
Masked Somatic Mutation	msm	Open

Methylation Beta Value	mbv	Open
miRNA Expression Quantification	meq	Open
Aligned Reads	ar	Controlled
Aggregated Somatic Mutation	agsm	Controlled
Annotated Somatic Mutation	ansm	Controlled
Raw Simple Somatic Mutation	rssm	Controlled

Data granularity

We consider the aliquot as the basic data granularity; it is the elementary unit of GDC (TCGA), which identifies a single experiment on a tissue. The aliquot is the unit of analysis for GDC genomic data. Aliquots are the products shipped by the Biospecimen Core Resources to analysis centers. A Biospecimen Core Resource (BCR) is a TCGA center where samples are carefully catalogued, processed, quality-checked and stored along with participant clinical information.
More details are available at https://docs.gdc.cancer.gov/Data/Data_Model/GDC_Data_Model/.
In GDC aliquots are encoded with the Universal Unique Identifier (UUID), a 128-bit number used to uniquely identify an object or entity in a system. More details about the UUID are available at https://docs.gdc.cancer.gov/Encyclopedia/pages/UUID/. UUIDs are also used for identifying samples and patients in GDC. It is worth noting that the aliquot is encoded in the "gdc__aliquots__aliquot_id" meta data attribute. See meta data section for further details. For indexing our output data, we use an internal ID called OpenGDC ID (precisely, manually_curated_opengdc_id), which is composed of the "gdc__aliquots__aliquot_id" concatenated with the acronym of the considered experiment, i.e., gdc__aliquots__aliquot_id-experiment_acronym. See subsection "Input data sets" for the acronyms associated with the experiments.

Output data

We provide the user with all the public GDC TCGA data sets properly converted in BED format.
In particular, for each data set the data are provided as follows:

(i) a .bed file for each aliquot UUID, containing the experiment data converted in BED / CSV / GTF / JSON / XML formats;
(ii) a .meta file for each aliquot, with meta data including the patient clinical and biospecimen data;
(iii) a header.schema file in XML format that describes the structure of the BED files.

Several other files containing general and statistical information about the experiments and metadata are produced as output (e.g., MD5 checksum files, metadata dictionary file, experiment information files, experiments annotations). We point the reader to the section Additional output files of this document for further details.

We use the 1-based (1-start or base-counted or fully-closed) genomic coordinate representation, as adopted in the GDC data files.

Missing values in case present in original data, are homogeneously labeled in the output format with the string "null" for numerical attributes, or with an empty string "" for text attributes.

Reference assembly

The genomic coordinates in all GDC and converted data sets refer to the human reference assembly GRCh38[5]. In particular[6]:
Genome Reference Consortium Human Build 38
Organism: Homo sapiens (human)
Submitter: Genome Reference Consortium
Date: 2013/12/17
Assembly type: haploid-with-alt-loci
Assembly level: Chromosome
Genome representation: full
Synonyms: hg38
GenBank assembly accession: GCA_000001405.15 (replaced)
RefSeq assembly accession: GCF_000001405.26 (replaced).
Annotations source: GDC.h38 GENCODE v22 GTF annotation file

Tumor tags and tumor names

The following tumor tags of TCGA are available at GDC and correspond to the following tumor names:

TCGA-ACC	Adrenocortical carcinoma
TCGA-BLCA	Bladder Urothelial Carcinoma
TCGA-BRCA	Breast Invasive Carcinoma
TCGA-CESC	Cervical squamous cell carcinoma and endocervical adenocarcinoma
TCGA-CHOL	Cholangiocarcinoma
TCGA-COAD	Colon adenocarcinoma
TCGA-DLBC	Lymphoid Neoplasm Diffuse Large B-cell Lymphoma
TCGA-ESCA	Esophageal carcinoma
TCGA-GBM	Glioblastoma multiforme
TCGA-HNSC	Head and Neck squamous cell carcinoma
TCGA-KICH	Kidney Chromophobe
TCGA-KIRC	Kidney renal clear cell carcinoma

[5] https://www.ncbi.nlm.nih.gov/assembly/GCF_000001405.26
[6] https://gdc.cancer.gov/about-data/data-harmonization-and-generation/gdc-reference-files

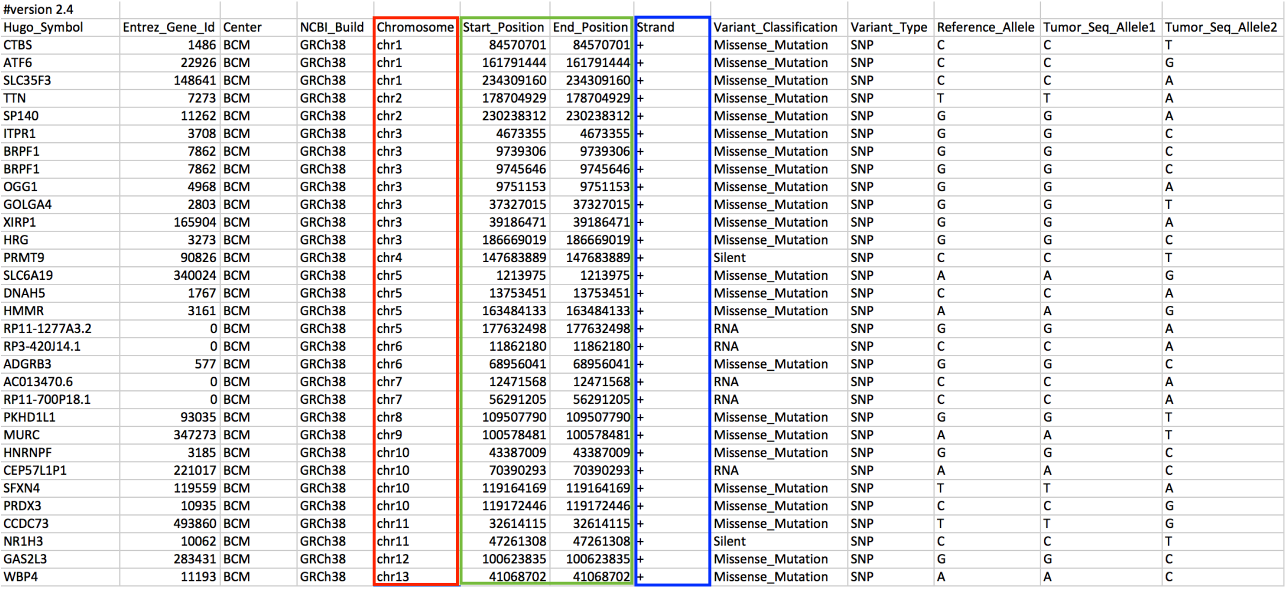
TCGA-KIRP	Kidney renal papillary cell carcinoma
TCGA-LAML	Acute Myeloid Leukemia
TCGA-LGG	Brain Lower Grade Glioma
TCGA-LIHC	Liver hepatocellular carcinoma
TCGA-LUAD	Lung adenocarcinoma
TCGA-LUSC	Lung squamous cell carcinoma
TCGA-MESO	Mesothelioma
TCGA-OV	Ovarian serous cystadenocarcinoma
TCGA-PAAD	Pancreatic adenocarcinoma
TCGA-PCPG	Pheochromocytoma and Paraganglioma
TCGA-PRAD	Prostate adenocarcinoma
TCGA-READ	Rectum adenocarcinoma
TCGA-SARC	Sarcoma
TCGA-SKCM	Skin Cutaneous Melanoma
TCGA-STAD	Stomach adenocarcinoma
TCGA-TGCT	Testicular Germ Cell Tumors
TCGA-THCA	Thyroid carcinoma
TCGA-THYM	Thymoma
TCGA-UCEC	Uterine Corpus Endometrial Carcinoma
TCGA-UCS	Uterine Carcinosarcoma
TCGA-UVM	Uveal Melanoma

Masked Somatic Mutation

This type of Next Generation Sequencing (NGS) experiment discovers mutations by aligning DNA sequences derived from tumor samples to sequences derived from normal samples and a reference sequence. A Mutation Annotation Format (MAF) file is used to specify, for each sample, the discovered putative or validated mutations and to categorize those mutations (SNP, deletion, or insertion) as somatic (originating in the tissue) or germline (originating from the germline), as well as to specify additional information for those mutations.
More details are available at https://docs.gdc.cancer.gov/Data/PDF/Data_UG.pdf and at https://gdc.cancer.gov/about-data/data-harmonization-and-generation/genomic-data-harmonization/high-level-data-generation/dna-seq-somatic-variation

Input: multiple MAF files for each tumor are provided by GDC, each with DNA-sequencing data; each of those files includes 125 attributes (columns), which are described at https://docs.gdc.cancer.gov/Data/File_Formats/MAF_Format/

Example of the first 13 attributes (columns) of a GDC MAF file



#version 2.4												
Hugo_Symbol	Entrez_Gene_Id	Center	NCBI_Build	Chromosome	Start_Position	End_Position	Strand	Variant_Classification	Variant_Type	Reference_Allele	Tumor_Seq_Allele1	Tumor_Seq_Allele2
CTBS	1486	BCM	GRCh38	chr1	84570701	84570701	+	Missense_Mutation	SNP	C	C	T
ATF6	22926	BCM	GRCh38	chr1	161791444	161791444	+	Missense_Mutation	SNP	C	C	G
SLC35F3	148641	BCM	GRCh38	chr1	234309160	234309160	+	Missense_Mutation	SNP	C	C	A
TTN	7273	BCM	GRCh38	chr2	178704929	178704929	+	Missense_Mutation	SNP	T	T	A
SP140	11262	BCM	GRCh38	chr2	230238312	230238312	+	Missense_Mutation	SNP	G	G	A
ITPR1	3708	BCM	GRCh38	chr3	4673355	4673355	+	Missense_Mutation	SNP	G	G	C
BRPF1	7862	BCM	GRCh38	chr3	9739306	9739306	+	Missense_Mutation	SNP	G	G	C
BRPF1	7862	BCM	GRCh38	chr3	9745646	9745646	+	Missense_Mutation	SNP	G	G	C
OGG1	4968	BCM	GRCh38	chr3	9751153	9751153	+	Missense_Mutation	SNP	G	G	A
GOLGA4	2803	BCM	GRCh38	chr3	37327015	37327015	+	Missense_Mutation	SNP	G	G	T
XIRP1	165904	BCM	GRCh38	chr3	39186471	39186471	+	Missense_Mutation	SNP	G	G	A
HRG	3273	BCM	GRCh38	chr3	186669019	186669019	+	Missense_Mutation	SNP	G	G	C
PRMT9	90826	BCM	GRCh38	chr4	147683889	147683889	+	Silent	SNP	C	C	T
SLC6A19	340024	BCM	GRCh38	chr5	1213975	1213975	+	Missense_Mutation	SNP	A	A	G
DNAH5	1767	BCM	GRCh38	chr5	13753451	13753451	+	Missense_Mutation	SNP	C	C	A
HMMR	3161	BCM	GRCh38	chr5	163484133	163484133	+	Missense_Mutation	SNP	A	A	G
RP11-1277A3.2	0	BCM	GRCh38	chr5	177632498	177632498	+	RNA	SNP	G	G	A
RP3-420J14.1	0	BCM	GRCh38	chr6	11862180	11862180	+	RNA	SNP	C	C	A
ADGRB3	577	BCM	GRCh38	chr6	68956041	68956041	+	Missense_Mutation	SNP	G	G	C
AC013470.6	0	BCM	GRCh38	chr7	12471568	12471568	+	RNA	SNP	C	C	A
RP11-700P18.1	0	BCM	GRCh38	chr7	56291205	56291205	+	RNA	SNP	C	C	A
PKHD1L1	93035	BCM	GRCh38	chr8	109507790	109507790	+	Missense_Mutation	SNP	G	G	T
MURC	347273	BCM	GRCh38	chr9	100578481	100578481	+	Missense_Mutation	SNP	A	A	T
HNRNPF	3185	BCM	GRCh38	chr10	43387009	43387009	+	Missense_Mutation	SNP	G	G	C
CEP57L1P1	221017	BCM	GRCh38	chr10	70390293	70390293	+	RNA	SNP	A	A	C
SFXN4	119559	BCM	GRCh38	chr10	119164169	119164169	+	Missense_Mutation	SNP	T	T	A
PRDX3	10935	BCM	GRCh38	chr10	119172446	119172446	+	Missense_Mutation	SNP	C	C	G
CCDC73	493860	BCM	GRCh38	chr11	32614115	32614115	+	Missense_Mutation	SNP	T	T	G
NR1H3	10062	BCM	GRCh38	chr11	47261308	47261308	+	Silent	SNP	C	C	T
GAS2L3	283431	BCM	GRCh38	chr12	100623835	100623835	+	Missense_Mutation	SNP	G	G	C
WBP4	11193	BCM	GRCh38	chr13	41068702	41068702	+	Missense_Mutation	SNP	A	A	C

BED output format: a tab separated BED file, in which each original DNA-seq .maf file is converted, with the following 18 fields, the main ones in the original MAF file:

1. **chrom** (i.e., the name of the chromosome, e.g., "chr3", "chrY", "chr2_random", equal to the 5. field of the GDC MAF file)
2. **start** (i.e., the starting position of the feature in the chromosome or scaffold, e.g., 999, equal to the 6. field of the GDC MAF file)
3. **end** (i.e., the ending position of the feature in the chromosome or scaffold, e.g., 1000, equal to the 7. field of the GDC MAF file)

4. **strand** (i.e., the DNA strand where the feature is observed, either '+' or '-', equal to the 8. field of the GDC MAF file)
5. **gene_symbol** (i.e., the symbol of the gene related to the reported variant, if it exists, e.g., “HRG”, equal to the 1. field of the GDC MAF file)
6. **entrez_gene_id** (i.e., the Entrez gene ID of the gene related to the reported variant, if it exists, e.g., “3273”, equal to the 2. field of the GDC MAF file)
7. **variant_classification** (i.e., the classification of the reported variant, e.g., “Missense_Mutation”, equal to the 9. field of the GDC MAF file)
8. **variant_type** (i.e., the type of mutation, e.g., “INS”, equal to the 10. field of the GDC MAF file)
9. **reference_allele** (i.e., the plus strand reference allele at the variant position, e.g., “A”, equal to the 11. field of the GDC MAF file)
10. **tumor_seq_allele1** (i.e., the tumor sequencing (discovery) allele 1, e.g., “C”, equal to the 12. field of the GDC MAF file)
11. **tumor_seq_allele2** (i.e., the tumor sequencing (discovery) allele 2, e.g., “G”, equal to the 13. field of the GDC MAF file)
12. **dbsnp_rs** (i.e., the latest dbSNP rs ID, e.g., “rs12345” or “novel” if not present in dbSNP, equal to the 14. field of the GDC MAF file)
13. **tumor_sample_barcode** (i.e., the BCR aliquot barcode for the tumor sample, e.g., “TCGA-02-0021-01A-01D-0002-04”, equal to the 16. field of the GDC MAF file)
14. **matched_norm_sample_barcode** (i.e., the BCR aliquot barcode for the matched normal sample, e.g., “TCGA-02-0021-10A-01D-0002-04”, equal to the 17. field of the GDC MAF file)
15. **match_norm_seq_allele1** (i.e., the matched normal sequencing allele 1, e.g., “T”, equal to the 18. field of the GDC MAF file)
16. **match_norm_seq_allele2** (i.e., the matched normal sequencing allele 2, e.g., “ACGT”, equal to the 19. field of the GDC MAF file)
17. **tumor_sample_uuid** (i.e., the BCR aliquot UUID for the tumor sample, e.g., “b2804bb2-70f4-471a-b6db-70c0ef457df3”, equal to the 33. field of the GDC MAF file)
18. **matched_norm_sample_uuid** (i.e., the BCR aliquot UUID for the matched normal sample, e.g., “567e8487-e29b-32d4-a716-446655443246”, equal to the 34. field of the GDC MAF file)

Notes about GDC MAF format

- This format is not to be confused with the UCSC Multiple Alignment Format
- The GDC MAF format regards a tab-delimited file containing only somatic mutations (open access portion of the GDC Data Portal for the TCGA project)
- Mutations are discovered by aligning DNA sequences derived from tumor samples to sequences derived from normal samples and a reference sequence. A MAF file specifies, for each sample, the discovered putative or validated mutations and categorizes those mutations (SNP, deletion, or insertion) as somatic (originating in the tissue), as well as specifies additional information for those mutations.

- Types of specified somatic mutations:
  - Missense and nonsense mutation
  - Splice site mutation, defined as SNP within 2 bp of the splice junction
  - Silent mutation
  - Indel mutation, which overlaps the coding region or splice site of a gene or the targeted region of a genetic element of interest
  - Frameshift mutation
  - Mutation in regulatory regions
- Included SNPs:
  - Any germline SNP with validation status "unknown" is included
  - SNPs already validated in dbSNP are not included, since they are unlikely to be involved in cancer
- The 125 MAF format attributes (columns) are described at https://docs.gdc.cancer.gov/Data/File_Formats/MAF_Format/
- Column headers and values are case sensitive where specified
- Columns may allow null values (i.e., blank cells) and/or have enumerated values; when converted to BED format, null values for numeric columns (attributes) are marked with the "null" label, whereas those for not numeric (textual) columns (attributes) are left as blank cells

Gene Expression Quantification

GDC provides gene expression quantification data in three files for each aliquot:

- FPKM (i.e., Fragments Per Kilobase of transcript per Million mapped reads)
- FPKM-UQ (i.e., Upper Quartile normalized FPKM values)
- counts (i.e., raw mapping counts of reads mapped to each gene)

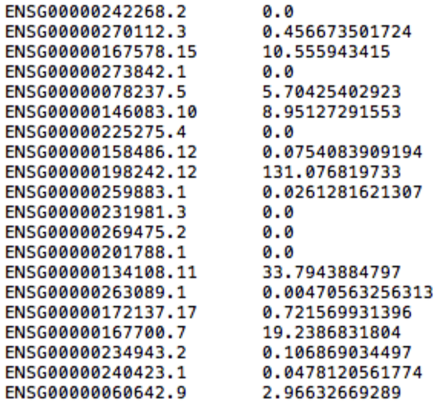
More details are described in the GDC Data User's Guide available at https://docs.gdc.cancer.gov/Data/PDF/Data_UG.pdf and at https://gdc.cancer.gov/about-data/data-harmonization-and-generation/genomic-data-harmonization/high-level-data-generation/rna-seq-quantification.

Input: FPKM file

One tab-delimited file is provided by GDC for each aliquot, with the following fields:

1. Gene_Ensembl (i.e., the Ensembl ID of the gene, including its version with "." notation);
2. FPKM (i.e., number of Fragments Per Kilobase of transcript per Million mapped reads).

FPKM file example



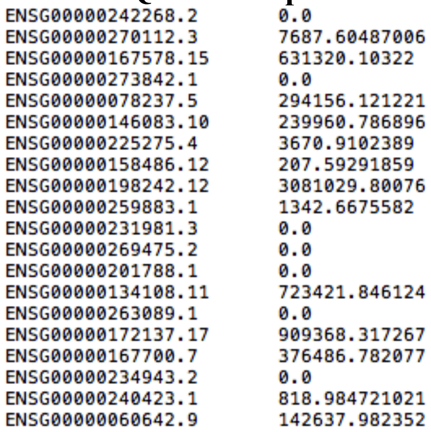
```
ENSG00000242268.2       0.0
ENSG00000270112.3       0.456673501724
ENSG00000167578.15      10.555943415
ENSG00000273842.1       0.0
ENSG00000078237.5       5.70425402923
ENSG00000146083.10      8.95127291553
ENSG00000225275.4       0.0
ENSG00000158486.12      0.0754083909194
ENSG00000198242.12      131.076819733
ENSG00000259883.1       0.0261281621307
ENSG00000231981.3       0.0
ENSG00000269475.2       0.0
ENSG00000201788.1       0.0
ENSG00000134108.11      33.7943884797
ENSG00000263089.1       0.00470563256313
ENSG00000172137.17      0.721569931396
ENSG00000167700.7       19.2386831804
ENSG00000234943.2       0.106869034497
ENSG00000240423.1       0.0478120561774
ENSG00000060642.9       2.96632669289
```

Input: FPKM-UQ file

Another tab-delimited file is provided by GDC for each aliquot, with the following fields:

1. Gene_Ensembl (i.e., the Ensembl ID of the gene, including its version with "." notation);
2. UQ-FPKM (i.e., Upper Quartile normalized FPKM value).

FPKM-UQ file example



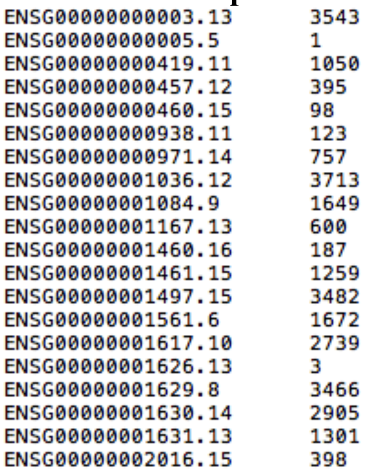
```
ENSG00000242268.2       0.0
ENSG00000270112.3       7687.60487006
ENSG00000167578.15      631320.10322
ENSG00000273842.1       0.0
ENSG00000078237.5       294156.121221
ENSG00000146083.10      239960.786896
ENSG00000225275.4       3670.9102389
ENSG00000158486.12      207.59291859
ENSG00000198242.12      3081029.80076
ENSG00000259883.1       1342.6675582
ENSG00000231981.3       0.0
ENSG00000269475.2       0.0
ENSG00000201788.1       0.0
ENSG00000134108.11      723421.846124
ENSG00000263089.1       0.0
ENSG00000172137.17      909368.317267
ENSG00000167700.7       376486.782077
ENSG00000234943.2       0.0
ENSG00000240423.1       818.984721021
ENSG00000060642.9       142637.982352
```

Input: **Counts file**

Another tab-delimited file is provided by GDC for each aliquot, with the following fields:

1. Gene_Ensembl (i.e., the Ensembl ID of the gene, including its version with "." notation);
2. counts (i.e., the number of reads aligned to each gene, calculated by HT-seq).

Counts file example



```
ENSG00000000003.13      3543
ENSG00000000005.5       1
ENSG00000000419.11      1050
ENSG00000000457.12      395
ENSG00000000460.15      98
ENSG00000000938.11      123
ENSG00000000971.14      757
ENSG00000001036.12      3713
ENSG00000001084.9       1649
ENSG00000001167.13      600
ENSG00000001460.16      187
ENSG00000001461.15      1259
ENSG00000001497.15      3482
ENSG00000001561.6       1672
ENSG00000001617.10      2739
ENSG00000001626.13      3
ENSG00000001629.8       3466
ENSG00000001630.14      2905
ENSG00000001631.13      1301
ENSG00000002016.15      398
```

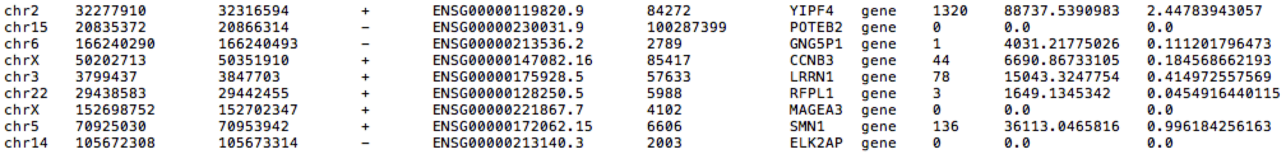
BED output format: We merge the three original GDC files in one single BED file with the following fields:

1. **chrom** (retrieved from GDC.h38 GENCODE v22 GTF annotation file[7] according to the Ensembl ID of the gene, completed with "chr", e.g., "chr2")

[7] *GDC.h38 GENCODE v22 GTF annotation file: https://api.gdc.cancer.gov/data/25aa497c-e615-4cb7-8751-71f744f9691f*

2. **start** (retrieved from GDC.h38 GENCODE v22 GTF annotation file[5] according to the Ensembl ID of the gene, e.g., 32277910)
3. **end** (retrieved from GDC.h38 GENCODE v22 GTF annotation file[5] according to the Ensembl ID of the gene, e.g., 32316594)
4. **strand** (retrieved from GDC.h38 GENCODE v22 GTF annotation file[5] according to the Ensembl ID of the gene, e.g., '+')
5. **ensembl_gene_id** (equal to the 1. field of any of the GDC gene expression quantification files, e.g., "ENSG00000119820.9")
6. **entrez_gene_id** (retrieved from the Genome annotation file of NCBI[8] according to the human gene symbol. If it is not found, then it is retrieved from the gene history file of NCBI[9] according to the human gene symbol. Otherwise, if it is not found from the NCBI sources, it is retrieved from HUGO Gene Nomenclature Committee (HGNC)[10] according to the human gene symbol, e.g., "YIPF4")
7. **gene_symbol** (retrieved from GDC.h38 GENCODE v22 GTF annotation file[5] according to the Ensembl ID of the gene, e.g., "YIPF4")
8. **type** (retrieved from GDC.h38 GENCODE v22 GTF annotation files[5] according to the Ensembl ID of the gene, e.g., "gene")
9. **htseq_count** (equal to the 2. field of the GDC counts file, e.g., 1320)
10. **fpkm_uq** (equal to the 2. field of the GDC FPKM-UQ file, e.g., 88737.5390983
11. **fpkm** (equal to the 2. field of the GDC FPKM file, e.g., 2.44783943057)

BED file example



```
chr2    32277910    32316594    +   ENSG00000119820.9    84272       YIPF4   gene  1320  88737.5390983  2.44783943057
chr15   20835372    20866314    -   ENSG00000230031.9    100287399   POTEB2  gene  0     0.0            0.0
chr6    166240290   166240493   -   ENSG00000213536.2    2789        GNG5P1  gene  1     4031.21775026  0.111201796473
chrX    50202713    50351910    +   ENSG00000147082.16   85417       CCNB3   gene  44    6690.86733105  0.184568662193
chr3    3799437     3847703     +   ENSG00000175928.5    57633       LRRN1   gene  78    15043.3247754  0.414972557569
chr22   29438583    29442455    +   ENSG00000128250.5    5988        RFPL1   gene  3     1649.1345342   0.0454916440115
chrX    152698752   152702347   +   ENSG00000221867.7    4102        MAGEA3  gene  0     0.0            0.0
chr5    70925030    70953942    +   ENSG00000172062.15   6606        SMN1    gene  136   36113.0465816  0.996184256163
chr14   105672308   105673314   -   ENSG00000213140.3    2003        ELK2AP  gene  0     0.0            0.0
```

[8] ftp://ftp.ncbi.nlm.nih.gov/genomes/H_sapiens/ARCHIVE/ANNOTATION_RELEASE.107/GFF/ref_GRCh38.p2_top_level.gff3.gz

[9] ftp://ftp.ncbi.nlm.nih.gov/gene/DATA/gene_history.gz

[10] Queries to HUGO Gene Nomenclature Committee (HGNC) are performed according to the following REST query http://rest.genenames.org/fetch/symbol/ followed by gene symbol, e.g., http://rest.genenames.org/fetch/symbol/BRCA1

Methylation Beta Value

A wide-spread NGS experiment is the large-scale analysis of DNA methylation, which consists in deep sequencing of bisulfite-treated DNA. DNA methylation can be defined as the covalent modification of cytosine bases at the C-5 position, generally within a CpG sequence context. If DNA methylation occurs in promoter regions, it is an epigenetic mark that represents the repression of the transcripts of the promoter gene.

More details are described in the GDC Data User's Guide available at https://docs.gdc.cancer.gov/Data/PDF/Data_UG.pdf and at https://docs.gdc.cancer.gov/Data/Bioinformatics_Pipelines/Methylation_LO_Pipeline/.

We consider both Illumina Infinium HumanMethylation27 (HM27) and HumanMethylation450 (HM450) DNA methylation platforms. They are used for measuring the level of methylation at 27,578 / 485,577 known CpG sites as beta values. Using probe sequence information provided in the manufacturer's manifest, HM27 and HM450 probes were remapped to the GRCh38 reference genome. The HM27 and HM450 manifest files are available at https://www.ncbi.nlm.nih.gov/geo/download/?acc=GPL8490&format=file&file=GPL8490%5FHumanMethylation27%5F270596%5Fv%2E1%2E2%2Ecsv%2Egz and ftp://webdata2:webdata2@ussd-ftp.illumina.com/downloads/ProductFiles/HumanMethylation450/HumanMethylation450_15017482_v1-2.csv, respectively.

These probe coordinates were then used to identify the associated transcripts from GENCODE v22, the associated CpG island (CGI), and the CpG sites' distance from each of these features. Multiple transcripts overlapping the target CpG were separated with semicolons. Beta values were inherited from existing TCGA Level 3 DNA methylation data (hg19-based) based on Probe IDs.

When DNA is methylated, the cytosines on each strand of a CpG dinucleotide are methylated (https://www.quora.com/How-are-epigenetic-mutations-passed-on-from-cell-to-cell-if-they-are-not-encoded-in-the-genome); we associate a strand to each methylated site based on the human gene symbol of the gene region where the CpG dinucleotide is located. If the human gene symbol is not available, for the strand we insert the * value (which indicates unspecified strand).

GDC reports for each methylated site a list of symbols of genes that are associated with it. The association is defined with methylations whose region (2 bp) is superimposed (for at least 1 base) to the gene region (gene body) or to a neighborhood of 1,500 bp upstream of the gene.

Input:

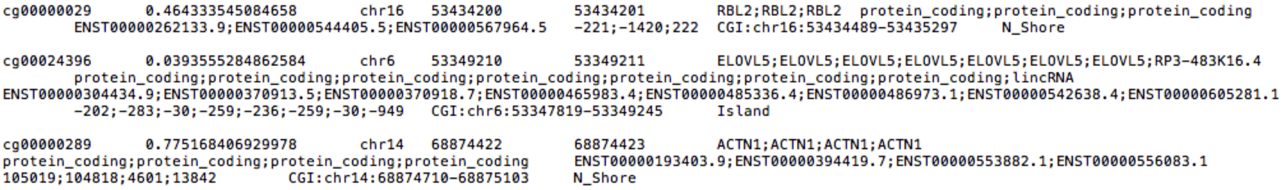
One tab-delimited file is provided by GDC for each aliquot, with the following fields:

1. composite_element_ref (i.e., the composite element reference, used to record the location of what is aligned to the considered assembly; it is an unique ID for the array probe associated with a CpG site; the IDs that begin with the prefix "cg" are Illumina probe IDs of CpG-targeting probes; the IDs that begin with the prefix "ch" are illumina probe IDs of non-CpG-targeting probes; the IDs that start with the prefix "rs" refer to methylated sites, which overlap well known SNPs, therefore NCBI SNP IDs are used);
2. beta_value (i.e., the ratio between the methylated array intensity and total array intensity, falling between 0 (lower levels of methylation) and 1 (higher levels of methylation); missing values (i.e., not measured or with unreliable measurement) are encoded with "NA");
3. chr (i.e., the chromosome in which the probe binding site is located);
4. start (i.e., the starting position of the probed CpG dinucleotide (a CpG island is where a cytosine nucleotide occurs next to a guanine nucleotide));
5. end (i.e., the ending position of the probed CpG dinucleotide (a CpG island is where a cytosine nucleotide occurs next to a guanine nucleotide));
6. gene_symbol (i.e., the symbol of each of the genes (can be more than one, separated by the ; char) associated with the CpG site. The association is defined with methylations whose region (2 bp) is superimposed (for at least 1 base) to the gene region (gene body) or to a neighborhood of 1,500 bp upstream of the gene. The same gene symbol is repeated if more than one transcript_id of the gene (reported in field 8) is associated with the methylation site.)
7. gene_type (i.e., a general classification for each associated gene (e.g., protein coding, miRNA, pseudogene), separated by the ; char);
8. transcript_id (i.e., Ensembl transcript ID of each transcript associated with the genes detailed above, separated by the ; char);
9. position_to_tss (i.e., distance in base pairs of the CpG site from each associated transcript's start site, separated by the ; char; negative values indicate that the CpG site is located downstream with respect to the TSS);
10. cgi_coordinate (CpG island coordinate, i.e., the start and end coordinates of the CpG island associated with the CpG site);
11. feature_type (i.e., the position of the CpG site in reference to the island: Island, or N_Shore, or S_Shore (0-2 kb upstream, or downstream from CGI), or N_Shelf, or S_Shelf (2-4 kbp upstream or downstream from CGI))
    CpG island shores are 0–2 kb from CGI, CpG island shelves are 2–4 kb from CGI, N stands for upstream, S for downstream. For more details the reader may refer to http://www.sciencedirect.com/science/article/pii/S0888754311001807.
    "Methylated cytosines can be in CpG islands, shores, shelves, open sea, and sites surrounding transcription sites [−200 to −1500 bp, 5′ untranslated region (UTR), and exons 1] for coding

genes as well as gene bodies and 3′ UTR and other/open sea regions derived from genome-wide association studies. Shores are considered regions 0–2 kb from CpG islands, shelves are regions 2–4 kb from CpG islands, and other/open sea regions are isolated CpG sites in the genome that do not have a specific designation.” In this last case the feature_type is not defined and encoded with “.”. [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3387424/]

Each row in the input file refers to a single CpG island.

Input example



```
cg00000029      0.464333545084658       chr16   53434200        53434201        RBL2;RBL2;RBL2  protein_coding;protein_coding;protein_coding
        ENST00000262133.9;ENST00000544405.5;ENST00000567964.5   -221;-1420;222  CGI:chr16:53434489-53435297     N_Shore

cg00024396      0.0393555284862584      chr6    53349210        53349211        ELOVL5;ELOVL5;ELOVL5;ELOVL5;ELOVL5;ELOVL5;ELOVL5;RP3-483K16.4
        protein_coding;protein_coding;protein_coding;protein_coding;protein_coding;protein_coding;protein_coding;lincRNA
ENST00000304434.9;ENST00000370913.5;ENST00000370918.7;ENST00000465983.4;ENST00000485336.4;ENST00000486973.1;ENST00000542638.4;ENST00000605281.1
        -202;-283;-30;-259;-236;-259;-30;-949   CGI:chr6:53347819-53349245      Island

cg00000289      0.775168406929978       chr14   68874422        68874423        ACTN1;ACTN1;ACTN1;ACTN1
protein_coding;protein_coding;protein_coding;protein_coding     ENST00000193403.9;ENST00000394419.7;ENST00000553882.1;ENST00000556083.1
105019;104818;4601;13842        CGI:chr14:68874710-68875103     N_Shore
```

BED output format: Tab separated BED file, in which the DNA methylation file is converted, with the following fields:

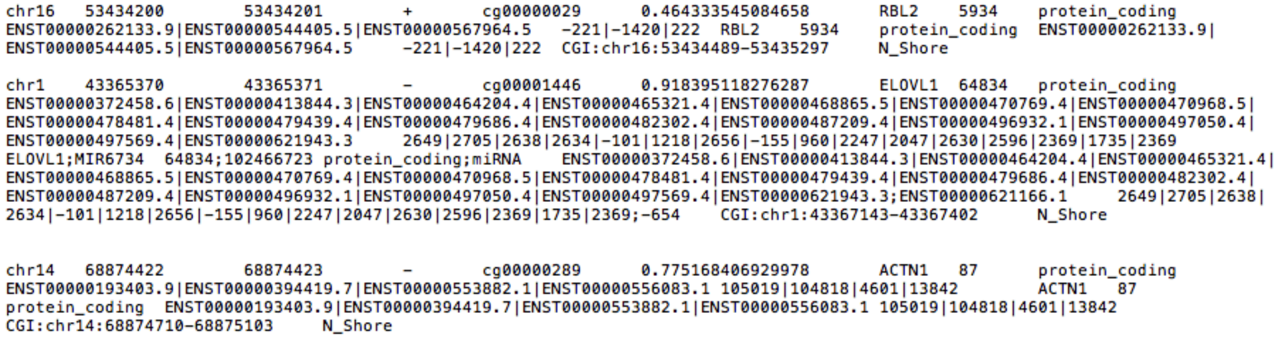
1. **chrom** (equal to the 3. field of the GDC DNA methylation file, i.e., the chromosome in which the probe binding site is located, e.g., “chr16”; it is worth to note that we filter out the methylation sites with missing genomic coordinates, which were originally encoded with “* -1 -1”.)
2. **start** (equal to the 4. field of the GDC DNA methylation file, i.e., the starting position of the probed CpG dinucleotide, since methylation involves a single base and the used genomic coordinate system is 1-based, e.g., 53434200)
3. **end** (equal to the 5. field of the GDC DNA methylation file, i.e., the ending position of the probed CpG dinucleotide since methylation involves a single base and the used genomic coordinate system is 1-based, e.g., 53434201)
4. **strand** (retrieved from GDC.h38 GENCODE v22 GTF annotation file[7], based on the human gene symbol provided in 7. field of this output file, e.g., ‘+’. If the human gene symbol is missing, then we insert the * character.)
5. **composite_element_ref** (equal to the 1. field of the GDC DNA methylation file, e.g., “cg00000092”. The list of all measured methylation region sites and their coordinates are available at ftp://geco.deib.polimi.it/opengdc/bed/_annotations/HumanMethylation27/ and ftp://geco.deib.polimi.it/opengdc/bed/_annotations/HumanMethylation450/)
6. **beta_value** (equal to the 2. field of the GDC DNA methylation file, e.g., 0.157004810973011; it is worth to note that we filter out the methylation sites with missing beta values (i.e., not measured or with unreliable measurement), which were originally encoded with “NA”.)

7. **gene_symbol** (the symbol of the gene region where the CpG dinucleotide is located, e.g., "RBL2"; retrieved from field 6 of the input file and GDC.h38 GENCODE v22 GTF annotation file[7]; if the CpG dinucleotide is outside a gene region, we report the gene symbol that is at minimum bp distance from the CpG dinucleotide, as retrieved from field 6 of the input file and GDC.h38 GENCODE v22 GTF annotation file[7]. If the field 12. of this output file is empty, no gene symbol is specified)
8. **entrez_gene_id** (retrieved from the Genome annotation file of NCBI[8] according to the human gene symbol. If it is not found, than it is retrieved from the gene history file of NCBI[9] according to the human gene symbol. Otherwise, if it is not found from the NCBI sources, it is retrieved from HUGO Gene Nomenclature Committee (HGNC)[10] according to the human gene symbol provided in the 6. field of this output file, e.g., 5934)
9. **gene_type** (type of gene provided in the 7. field of this output file, e.g., "protein_coding"; retrieved from the 7. field of the GDC DNA methylation file)
10. **ensembl_transcript_id** (Ensembl IDs of the transcripts related to the gene provided in the 7. field of this output file, e.g., "ENST00000544405.5|ENST00000262133.9", retrieved from the 8. field of the GDC DNA methylation file)
11. **position_to_tss** (distances in base pairs of the CpG site from each associated transcript's start site, related to the transcripts provided in the 10. field of this output file; negative values indicate that the CpG site is located downstream with respect to the TSS, e.g., "-221|-1420|222"; retrieved from the 9. field of the GDC DNA methylation file)
12. **all_gene_symbols** (equal to the 6. field of the GDC DNA methylation file, i.e., the symbol of each of the genes (can be more than one, separated by the ; char) associated with the CpG site, e.g., "RBL2, COX")
13. **all_entrez_gene_ids** (retrieved from HUGO Gene Nomenclature Committee (HGNC)[10] according to the gene symbols provided in the 12. field of this output file, e.g., 5934;1253;4861)
14. **all_gene_types** (equal to the 7. field of the GDC DNA methylation file, by taking into account the corresponding gene symbol (can be more than one, separated by the ; char) in field 12 of this output file, e.g., "protein_coding")
15. **all_ensembl_transcript_ids** (equal to the 8. field of the GDC DNA methylation file, i.e., Ensembl transcript ID of each transcript associated with the corresponding gene symbol (can be more than one, separated by the ; char) in field 12 of this output file, e.g., "ENST00000155840.8|ENST00000335475.5;ENST00000597346.1"), pipe delimits transcript IDs related to the same gene, semicolon the ones related to different genes
16. **all_positions_to_tss** (equal to the 9. field of the GDC DNA methylation file, i.e., distance in base pairs of the CpG site from each associated transcript's start site, by taking into account the corresponding gene symbol (can be more than one, separated by the ; char), negative values indicate that the CpG site is located downstream with respect to the TSS, e.g.,

"254241|237796;762"), pipe delimits positions_to_tss related to the same gene, semicolon the ones related to different genes

17. **cgi_coordinate** (equal to the 10. field of the GDC DNA methylation file, i.e., the start and end coordinates of the CpG island associated with the CpG site, e.g., "CGI:chr16:53434489-53435297")
18. **feature_type** (equal to the 11. field of the GDC DNA methylation file, i.e., the position of the CpG site in reference to the island, e.g., "N_Shore")

BED file example



```
chr16   53434200        53434201        +       cg00000029      0.464333545084658       RBL2    5934    protein_coding
ENST00000262133.9|ENST00000544405.5|ENST00000567964.5   -221|-1420|222  RBL2    5934    protein_coding  ENST00000262133.9|
ENST00000544405.5|ENST00000567964.5     -221|-1420|222  CGI:chr16:53434489-53435297     N_Shore

chr1    43365370        43365371        -       cg00001446      0.918395118276287       ELOVL1  64834   protein_coding
ENST00000372458.6|ENST00000413844.3|ENST00000464204.4|ENST00000465321.4|ENST00000468865.5|ENST00000470769.4|ENST00000470968.5|
ENST00000478481.4|ENST00000479439.4|ENST00000479686.4|ENST00000482302.4|ENST00000487209.4|ENST00000496932.1|ENST00000497050.4|
ENST00000497569.4|ENST00000621943.3     2649|2705|2638|2634|-101|1218|2656|-155|960|2247|2047|2630|2596|2369|1735|2369
ELOVL1;MIR6734  64834;102466723 protein_coding;miRNA    ENST00000372458.6|ENST00000413844.3|ENST00000464204.4|ENST00000465321.4|
ENST00000468865.5|ENST00000470769.4|ENST00000470968.5|ENST00000478481.4|ENST00000479439.4|ENST00000479686.4|ENST00000482302.4|
ENST00000487209.4|ENST00000496932.1|ENST00000497050.4|ENST00000497569.4|ENST00000621943.3;ENST00000621166.1     2649|2705|2638|
2634|-101|1218|2656|-155|960|2247|2047|2630|2596|2369|1735|2369;-654    CGI:chr1:43367143-43367402      N_Shore


chr14   68874422        68874423        -       cg00000289      0.775168406929978       ACTN1   87      protein_coding
ENST00000193403.9|ENST00000394419.7|ENST00000553882.1|ENST00000556083.1 105019|104818|4601|13842        ACTN1   87
protein_coding  ENST00000193403.9|ENST00000394419.7|ENST00000553882.1|ENST00000556083.1 105019|104818|4601|13842
CGI:chr14:68874710-68875103     N_Shore
```

Copy Number Segment and Masked Copy Number Segment

A copy number variation (CNV) is a variation in the number of copies of a given genomic segment per cell.
More details are described in the GDC Data User's Guide available at https://docs.gdc.cancer.gov/Data/PDF/Data_UG.pdf and at https://docs.gdc.cancer.gov/Data/Bioinformatics_Pipelines/CNV_Pipeline/.

Two different data types (both related to CNVs) are provided by GDC:

a) Copy Number Segment (includes both germline and somatic CNVs)
b) Masked Copy Number Segment (includes only somatic CNVs)

For the Copy Number Segment data type, the experiments have the suffix "grch38.seg" and they include both germline and somatic CNVs. Instead, for the Masked Copy Number Segment data type, the suffix for each experiment is "nocnv_grch38.seg" and it includes only somatic CNVs.

The internal representation of the files for both Copy Number Segment and Masked Copy Number Segment is the same. This is the reason why the following Input and Output paragraph is reported only once.

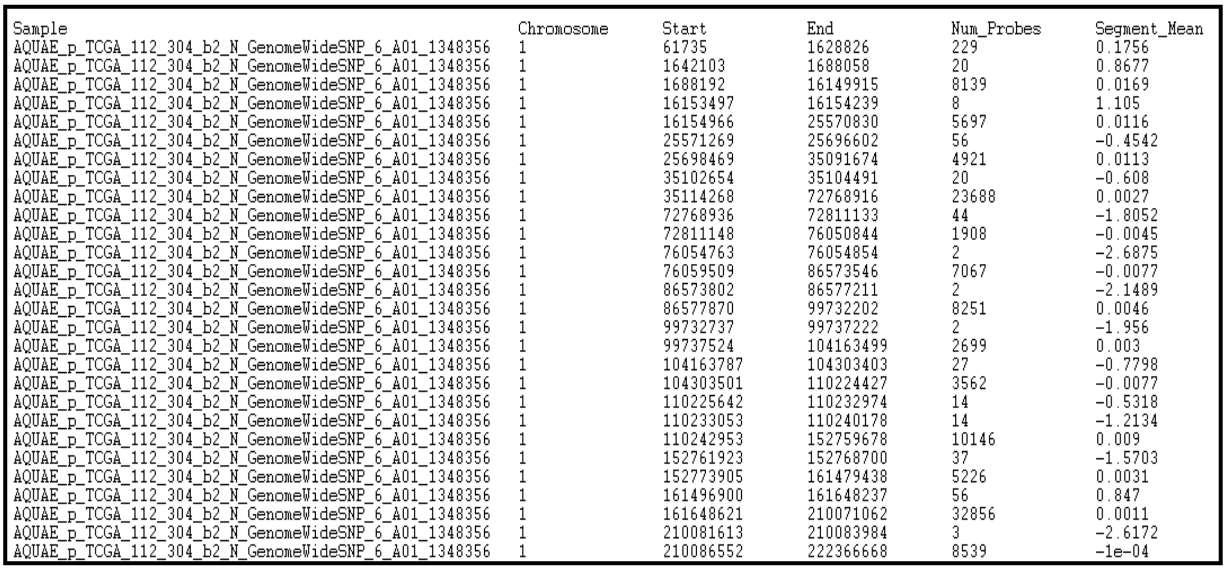
Input:
A single experiment is represented by a tab-delimited file with the following fields:

1. Sample (i.e., the GDC internal sample ID)
2. Chromosome (i.e., the name or number of the chromosome where the CNV is located)
3. Start (i.e., the starting position of the CNV feature in the chromosome)
4. End (i.e., the ending position of the CNV feature in the chromosome)
5. Num_Probes (i.e., the number of consecutive probes that comprise the genome segment with the CNV)
6. Segment_Mean (i.e., the estimated Copy Number (CN) ratio for the segment, that is the $\log_2$ ratio of the tumor intensity of CN to the normal intensity of CN; use $(2^{\text{Segment\_Mean}}) * 2$ to convert to absolute CN)[11]

Each row in the input file refers to a single CNV.

[11] https://www.biostars.org/p/112310/

Input example

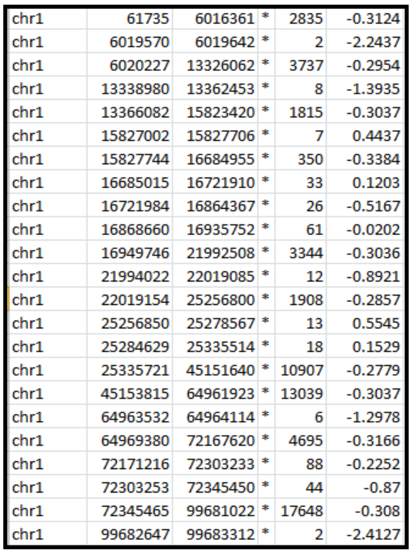


Sample	Chromosome	Start	End	Num_Probes	Segment_Mean
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	61735	1628826	229	0.1756
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	1642103	1688058	20	0.8677
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	1688192	16149915	8139	0.0169
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	16153497	16154239	8	1.105
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	16154966	25570830	5697	0.0116
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	25571269	25696602	56	-0.4542
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	25698469	35091674	4921	0.0113
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	35102654	35104491	20	-0.608
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	35114268	72768916	23688	0.0027
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	72768936	72811133	44	-1.8052
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	72811148	76050844	1908	-0.0045
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	76054763	76054854	2	-2.6875
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	76059509	86573546	7067	-0.0077
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	86573802	86577211	2	-2.1489
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	86577870	99732202	8251	0.0046
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	99732737	99737222	2	-1.956
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	99737524	104163499	2699	0.003
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	104163787	104303403	27	-0.7798
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	104303501	110224427	3562	-0.0077
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	110225642	110232974	14	-0.5318
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	110233053	110240178	14	-1.2134
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	110242953	152759678	10146	0.009
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	152761923	152768700	37	-1.5703
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	152773905	161479438	5226	0.0031
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	161496900	161648237	56	0.847
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	161648621	210071062	32856	0.0011
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	210081613	210083984	3	-2.6172
AQUAE_p_TCGA_112_304_b2_N_GenomeWideSNP_6_A01_1348356	1	210086552	222366668	8539	-1e-04

BED output format: Tab separated BED file, in which the CNV file is converted, with the following fields:

1. **chrom** (equal to the 2. field of the GDC CNV file, e.g., “1”)
2. **start** (equal to the 3. field of the GDC CNV file, e.g., 61735)
3. **end** (equal to the 4. field of the GDC CNV file, e.g., 1628826)
4. **strand** (unknown, set to ‘*’)
5. **num_probes** (equal to the 5. field of the GDC CNV file, e.g., 229)
6. **segment_mean** (equal to the 6. field of the GDC CNV file, e.g., 0.1756)

BED file example



chr1	61735	6016361	*	2835	-0.3124
chr1	6019570	6019642	*	2	-2.2437
chr1	6020227	13326062	*	3737	-0.2954
chr1	13338980	13362453	*	8	-1.3935
chr1	13366082	15823420	*	1815	-0.3037
chr1	15827002	15827706	*	7	0.4437
chr1	15827744	16684955	*	350	-0.3384
chr1	16685015	16721910	*	33	0.1203
chr1	16721984	16864367	*	26	-0.5167
chr1	16868660	16935752	*	61	-0.0202
chr1	16949746	21992508	*	3344	-0.3036
chr1	21994022	22019085	*	12	-0.8921
chr1	22019154	25256800	*	1908	-0.2857
chr1	25256850	25278567	*	13	0.5545
chr1	25284629	25335514	*	18	0.1529
chr1	25335721	45151640	*	10907	-0.2779
chr1	45153815	64961923	*	13039	-0.3037
chr1	64963532	64964114	*	6	-1.2978
chr1	64969380	72167620	*	4695	-0.3166
chr1	72171216	72303233	*	88	-0.2252
chr1	72303253	72345450	*	44	-0.87
chr1	72345465	99681022	*	17648	-0.308
chr1	99682647	99683312	*	2	-2.4127

miRNA Expression Quantification

miRNA-seq data are derived from the sequencing of micro RNAs (miRNA). They contain information about both nucleotide sequence and expression. More details are described in the GDC Data User's Guide available at https://docs.gdc.cancer.gov/Data/PDF/Data_UG.pdf and at https://docs.gdc.cancer.gov/Data/Bioinformatics_Pipelines/miRNA_Pipeline/.

One file for each aliquot is provided by GDC, containing the expression calculated based on all reads aligning to a particular miRNA.

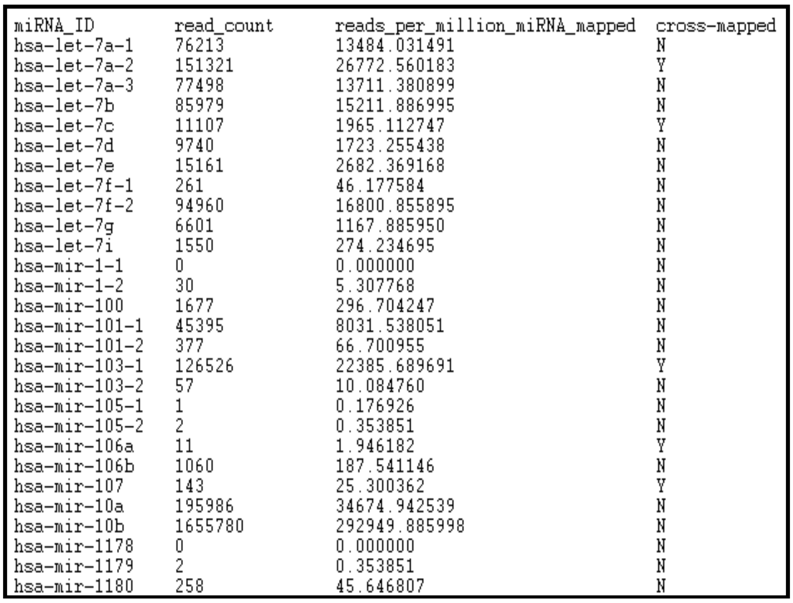
Input:

One tab-delimited file is provided by GDC for each aliquot, with the following fields:

1. miRNA_ID (i.e., a valid miRBase ID (http://www.mirbase.org/))
2. read_count (i.e., the sum of fractions of reads that mapped to a miRNA)
3. reads_per_million_miRNA_mapped (i.e., normalized read counts)
4. cross-mapped (i.e., cross-mapped to other miRNA forms (Y or N))

Each row in the input file refers to a single miRNA.

Input example



```
miRNA_ID        read_count      reads_per_million_miRNA_mapped  cross-mapped
hsa-let-7a-1    76213           13484.031491                    N
hsa-let-7a-2    151321          26772.560183                    Y
hsa-let-7a-3    77498           13711.380899                    N
hsa-let-7b      85979           15211.886995                    N
hsa-let-7c      11107           1965.112747                     Y
hsa-let-7d      9740            1723.255438                     N
hsa-let-7e      15161           2682.369168                     N
hsa-let-7f-1    261             46.177584                       N
hsa-let-7f-2    94960           16800.855895                    N
hsa-let-7g      6601            1167.885950                     N
hsa-let-7i      1550            274.234695                      N
hsa-mir-1-1     0               0.000000                        N
hsa-mir-1-2     30              5.307768                        N
hsa-mir-100     1677            296.704247                      N
hsa-mir-101-1   45395           8031.538051                     N
hsa-mir-101-2   377             66.700955                       N
hsa-mir-103-1   126526          22385.689691                    Y
hsa-mir-103-2   57              10.084760                       N
hsa-mir-105-1   1               0.176926                        N
hsa-mir-105-2   2               0.353851                        N
hsa-mir-106a    11              1.946182                        Y
hsa-mir-106b    1060            187.541146                      N
hsa-mir-107     143             25.300362                       Y
hsa-mir-10a     195986          34674.942539                    N
hsa-mir-10b     1655780         292949.885998                   N
hsa-mir-1178    0               0.000000                        N
hsa-mir-1179    2               0.353851                        N
hsa-mir-1180    258             45.646807                       N
```

BED output format: Tab separated BED file, in which the miRNA-seq quantification file is converted, with the following fields:

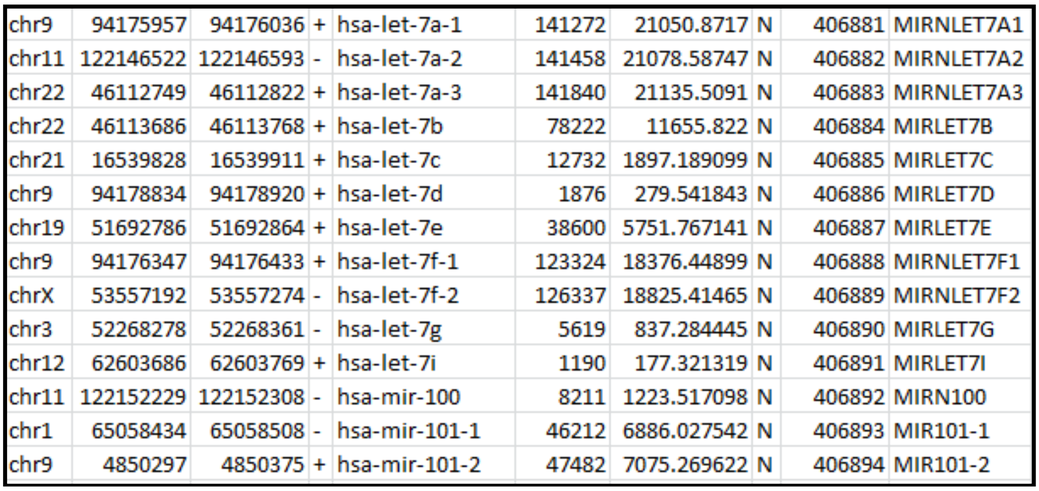
1. **chrom** (retrieved from miRBase database[12], according to the miRNA ID provided in field 5, e.g., “chr9”)
2. **start** (retrieved from miRBase database[12], according to the miRNA ID provided in field 5, e.g., 94175957)
3. **end** (retrieved from miRBase database[12], according to the miRNA ID provided in field 5, e.g., 94176036)
4. **strand** (retrieved from miRBase database[12], according to the miRNA ID provided in field 5, e.g., ‘+’)
5. **mirna_id** (equal to the 1. field of the GDC miRNA-seq file, e.g., “hsa-let-7a-1”)
6. **read_count** (equal to the 2. field of the GDC miRNA-seq file, e.g., 29726)
7. **reads_per_million_mirna_mapped** (equal to the 3. field of the GDC miRNA-seq file, e.g., 12429.699816)
8. **cross-mapped** (equal to the 4. field of the GDC miRNA-seq file, e.g., ‘N’)
9. **entrez_gene_id** (retrieved from HUGO Gene Nomenclature Committee (HGNC)[13] starting from the mirna_id provided in field 5)
10. **gene_symbol** (retrieved from HUGO Gene Nomenclature Committee (HGNC)[14] starting from the entrez_gene_id retrieved in field 9)

[12] Used GRCh38 data are retrieved from the version 21 of the miRBase database at ftp://mirbase.org/pub/mirbase/21/

[13] Queries to HUGO Gene Nomenclature Committee (HGNC) are performed according to the following rest query http://rest.genenames.org/fetch/hgnc_id/ followed by the **hgnc_id**; the **hgnc_id** is also retrieved from HUGO starting from the **mirna_id** provided in field 1 of the input file

[14] Queries to HUGO Gene Nomenclature Committee (HGNC) are performed according to the following REST query http://rest.genenames.org/fetch/entrez_id/ followed by the **entrez id**

BED file example



chr9	94175957	94176036	+	hsa-let-7a-1	141272	21050.8717	N	406881	MIRNLET7A1
chr11	122146522	122146593	-	hsa-let-7a-2	141458	21078.58747	N	406882	MIRNLET7A2
chr22	46112749	46112822	+	hsa-let-7a-3	141840	21135.5091	N	406883	MIRNLET7A3
chr22	46113686	46113768	+	hsa-let-7b	78222	11655.822	N	406884	MIRLET7B
chr21	16539828	16539911	+	hsa-let-7c	12732	1897.189099	N	406885	MIRLET7C
chr9	94178834	94178920	+	hsa-let-7d	1876	279.541843	N	406886	MIRLET7D
chr19	51692786	51692864	+	hsa-let-7e	38600	5751.767141	N	406887	MIRLET7E
chr9	94176347	94176433	+	hsa-let-7f-1	123324	18376.44899	N	406888	MIRNLET7F1
chrX	53557192	53557274	-	hsa-let-7f-2	126337	18825.41465	N	406889	MIRNLET7F2
chr3	52268278	52268361	-	hsa-let-7g	5619	837.284445	N	406890	MIRLET7G
chr12	62603686	62603769	+	hsa-let-7i	1190	177.321319	N	406891	MIRLET7I
chr11	122152229	122152308	-	hsa-mir-100	8211	1223.517098	N	406892	MIRN100
chr1	65058434	65058508	-	hsa-mir-101-1	46212	6886.027542	N	406893	MIR101-1
chr9	4850297	4850375	+	hsa-mir-101-2	47482	7075.269622	N	406894	MIR101-2

Isoform Expression Quantification

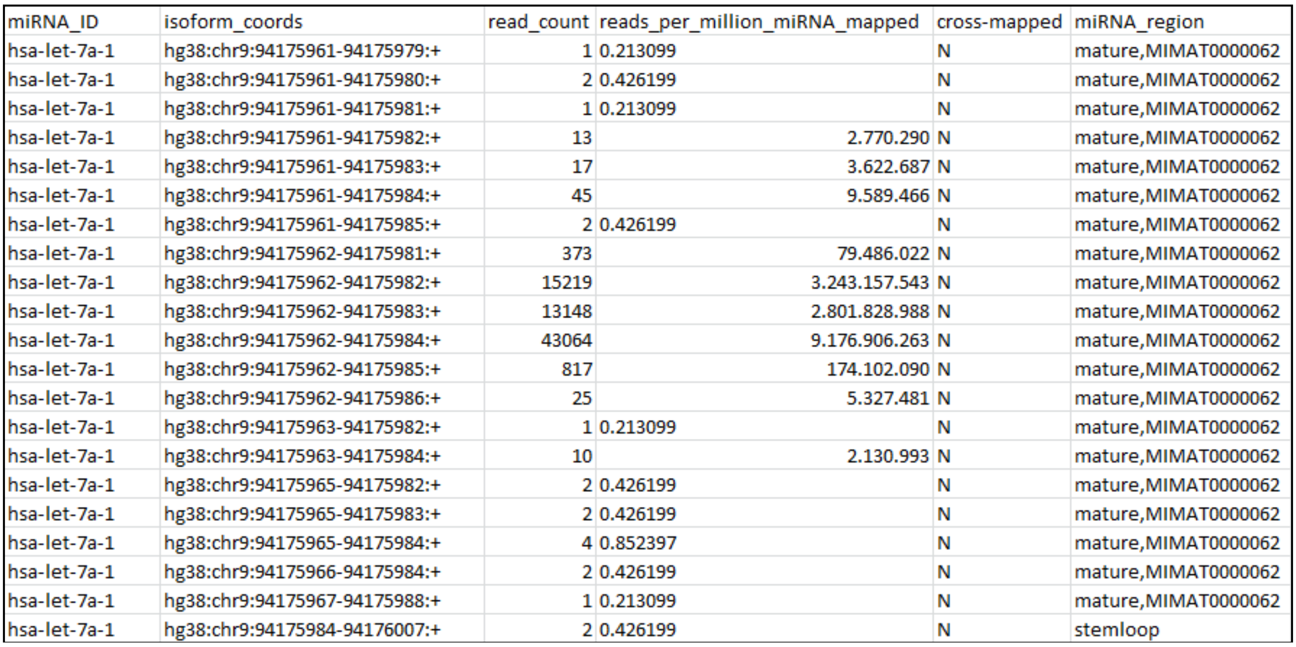
The miRNA Isoform Expression Quantification data contain expression profiles calculated for each individual miRNA sequence isoform observed.
More details are described in the GDC Data User's Guide available at https://docs.gdc.cancer.gov/Data/PDF/Data_UG.pdf and at https://docs.gdc.cancer.gov/Data/Bioinformatics_Pipelines/miRNA_Pipeline/.
GDC provides one file for each aliquot.

Input:
One tab-delimited file is provided by GDC for each aliquot, with the following fields:

1. miRNA_ID (i.e., a valid miRBase ID (http://www.mirbase.org/))
2. isoform_coords (i.e., Alignment coordinates as <version>:<Chromosome>:<Start position>-<End position>:<Strand>)
3. read_count (i.e., count of raw reads that mapped to a miRNA isoform)
4. reads_per_million_miRNA_mapped (i.e., millions of reads that mapped to a miRNA isoform)
5. cross-mapped (i.e., cross-mapped to other miRNA forms (Y or N))
6. miRNA_region (i.e., miRBase accession number of a class of miRNA sequence, e.g., mature, stemloop, ...)

Each row in the input file refers to a single isoform.

Input example

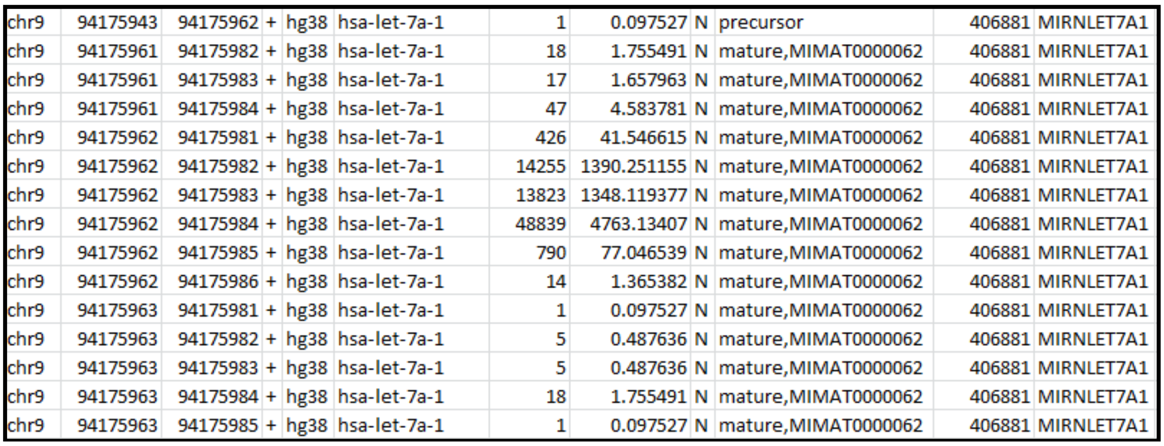


miRNA_ID	isoform_coords	read_count	reads_per_million_miRNA_mapped	cross-mapped	miRNA_region
hsa-let-7a-1	hg38:chr9:94175961-94175979:+	1	0.213099	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175961-94175980:+	2	0.426199	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175961-94175981:+	1	0.213099	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175961-94175982:+	13	2.770.290	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175961-94175983:+	17	3.622.687	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175961-94175984:+	45	9.589.466	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175961-94175985:+	2	0.426199	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175962-94175981:+	373	79.486.022	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175962-94175982:+	15219	3.243.157.543	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175962-94175983:+	13148	2.801.828.988	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175962-94175984:+	43064	9.176.906.263	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175962-94175985:+	817	174.102.090	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175962-94175986:+	25	5.327.481	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175963-94175982:+	1	0.213099	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175963-94175984:+	10	2.130.993	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175965-94175982:+	2	0.426199	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175965-94175983:+	2	0.426199	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175965-94175984:+	4	0.852397	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175966-94175984:+	2	0.426199	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175967-94175988:+	1	0.213099	N	mature,MIMAT0000062
hsa-let-7a-1	hg38:chr9:94175984-94176007:+	2	0.426199	N	stemloop

BED output format: Tab separated BED file, in which the miRNA-seq Isoform quantification file is converted, with the following fields:

1. **chrom** (retrieved from the 2. field of the GDC miRNA-seq file, part just after the first ":", e.g., "chr9")
2. **start** (retrieved from the 2. field of the GDC miRNA-seq file, part just after the second ":", e.g., 96938243)
3. **end** (retrieved from the 2. field of the GDC miRNA-seq file, part just before the third ":", e.g., 96938264)
4. **strand** (retrieved from the 2. field of the GDC miRNA-seq file, part just after the third ":", e.g., '+')
5. **genome_version** (retrieved from the 2. field of the GDC miRNA-seq file, part just before the first ":", e.g., "hg38")
6. **mirna_id** (equal to the 1. field of the GDC miRNA-seq file, e.g., "has-let-7a-1")
7. **read_count** (equal to the 3. field of the GDC miRNA-seq file, e.g., 4)
8. **reads_per_million_mirna_mapped** (equal to the 4. field of the GDC miRNA-seq file, e.g., 0.707702)
9. **cross-mapped** (equal to the 5. field of the GDC miRNA-seq file, e.g., 'N')
10. **mirna_region** (equal to the 6. field of the GDC miRNA-seq file, e.g., "mature, MIMAT0000062")
11. **entrez_gene_id** (retrieved from HUGO Gene Nomenclature Committee (HGNC)[13] starting from the **mirna_id** provided in field 6)
12. **gene_symbol** (retrieved from HUGO Gene Nomenclature Committee (HGNC)[14] starting from the **entrez_gene_id** provided in field 11)

BED file example



chr9	94175943	94175962	+	hg38	hsa-let-7a-1	1	0.097527	N	precursor	406881	MIRNLET7A1
chr9	94175961	94175982	+	hg38	hsa-let-7a-1	18	1.755491	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175961	94175983	+	hg38	hsa-let-7a-1	17	1.657963	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175961	94175984	+	hg38	hsa-let-7a-1	47	4.583781	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175962	94175981	+	hg38	hsa-let-7a-1	426	41.546615	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175962	94175982	+	hg38	hsa-let-7a-1	14255	1390.251155	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175962	94175983	+	hg38	hsa-let-7a-1	13823	1348.119377	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175962	94175984	+	hg38	hsa-let-7a-1	48839	4763.13407	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175962	94175985	+	hg38	hsa-let-7a-1	790	77.046539	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175962	94175986	+	hg38	hsa-let-7a-1	14	1.365382	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175963	94175981	+	hg38	hsa-let-7a-1	1	0.097527	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175963	94175982	+	hg38	hsa-let-7a-1	5	0.487636	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175963	94175983	+	hg38	hsa-let-7a-1	5	0.487636	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175963	94175984	+	hg38	hsa-let-7a-1	18	1.755491	N	mature,MIMAT0000062	406881	MIRNLET7A1
chr9	94175963	94175985	+	hg38	hsa-let-7a-1	1	0.097527	N	mature,MIMAT0000062	406881	MIRNLET7A1

Meta data: Clinical and Biospecimen Supplements and Genomic Data Commons API

Clinical and Biospecimen Supplements contain information about the patients (e.g., gender, race, weight, vital status, treatment, etc.) and the experiments conducted on normal and/or tumoral tissues of such patients (e.g., experiment name, disease type, tissue type, etc.), respectively.
More details about the attributes contained in Clinical Supplement data are available at https://gdc.cancer.gov/about-data/data-harmonization-and-generation/clinical-data-harmonization.
The attributes contained in Biospecimen Supplement data are listed and explained at https://gdc.cancer.gov/about-data/data-harmonization-and-generation/biospecimen-data-harmonization. The reader may also refer to the GDC Data User's Guide available at https://docs.gdc.cancer.gov/Data/PDF/Data_UG.pdf.

As a novelty, with respect to the previous TCGA release, GDC has disclosed the new GDC Data Model, a central method of organization of all data artifacts (i.e., files and entities) ingested by the GDC. The interested reader may see for details: https://docs.gdc.cancer.gov/Data/Data_Model/GDC_Data_Model/ and https://gdc.cancer.gov/developers/gdc-data-model/gdc-data-model-components.
The GDC Data Dictionary defines components of the GDC Data Model and relationships between them (https://docs.gdc.cancer.gov/Data_Dictionary/viewer/). Note that an equivalent version of documentation has been realized in tabular form by the Cancer Genomics Cloud – Seven Bridges (https://docs.cancergenomicscloud.org/docs/tcga-grch38-metadata).
In addition to the Clinical and Biospecimen Supplements, GDC provides access to the properties defined in the GDC Data Dictionary through its APIs.

Input

We consider three different sources to compose the final outcome of meta data.

1. **Clinical and Biospecimen Supplements**

   For the TCGA project GDC provides two XML files for each patient, the first one (Clinical) containing patient clinical data, the second one (Biospecimen) containing specimen data. An example of these files is available at:
   1. Clinical – https://api.gdc.cancer.gov/data/0bf20449-4129-4183-80ad-5e1eec2f84ea
   2. Biospecimen – https://api.gdc.cancer.gov/data/1be29e3c-c23d-4870-9329-972a28ccf160

2. **GDC API responses**

   For TCGA project GDC provides a wide number of fields related to each file, which can be

requested using RESTful APIs. A User Guide introduces the functionalities of "Search and Retrieval" in GDC APIs (https://docs.gdc.cancer.gov/API/Users_Guide/Search_and_Retrieval/). The complete list of fields that can be requested is contained in: https://docs.gdc.cancer.gov/API/Users_Guide/Appendix_A_Available_Fields/. The set considered in OpenGDC is displayed under the section "File Fields".
Note that meta data available through this platform have been standardized according to The NIH Common Data Elements (CDE, https://cde.nlm.nih.gov/cde/search) rules. A number of attributes presents a "CDE" code that references a term in the controlled vocabularies curated in the CDE Repository.

3. Manually curated meta data

OpenGDC adds additional meta data attributes, within a specific group named `manually_curated`. These attributes are not present in the input files, instead they are calculated within the OpenGDC system.

Meta data output format:
One meta data tab-delimited (.meta) file for each aliquot, whose rows contain all the meta data attribute-value pairs for the specific aliquot, with each attribute fully specified through the double underscore ("__") delimited composition of the name of the group/subgroup it belongs to and the name of the attribute. It is worth noting that every attribute name contained in a .meta file is codified to be a valid Java variable. This characteristic is required for each attribute to be correctly interpreted as valid search key. The name of these files corresponds to the aliquot ID of a single experiment concatenated with the acronym of the considered experiment, e.g., `007a5a35-5614-52d3-8393-7642ecf84933-geq.bed.meta`, where "geq" is the acronym of the considered experiment and stands for "gene expression quantification". See subsection "Input data sets" of this document for the acronyms associated with the experiments. When no experiment is associated with the meta data file, then we use the acronym "xxx", e.g., `0003c0e6-4e9e-544e-8ee7-55749e121895-xxx.bed.meta`. Not all GDC experiment files are released, therefore we can find some meta data not associated with experiments.

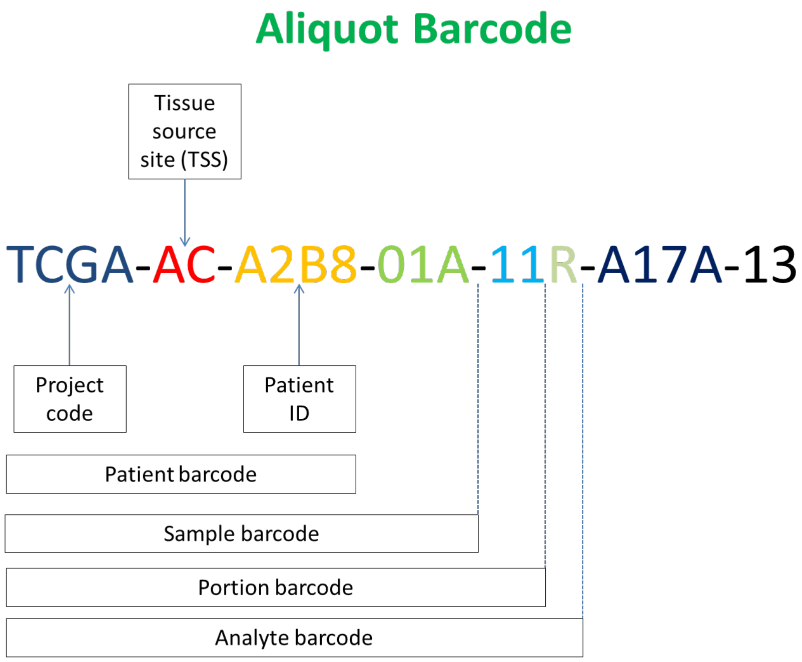
Meta data in the TCGA project: from Supplements
The Clinical and Biospecimen Supplements contain a number of groups (each attribute is defined as the subgroup of pertinence followed by the specific name of the attribute, e.g., `biospecimen__admin` followed by `disease_code`, which results in `biospecimen__admin__disease_code`). The following table describes the most important groups:

biospecimen__admin	Specifies properties related to the management of the specimen
biospecimen__bio	Specifies properties related to the biological aspects of the specimen
biospecimen__shared	Specifies properties of the specimen shared among all cancer types
clinical__admin	Specifies properties related to the management of the clinical aspects
clinical__clin_shared	Specifies clinical properties shared among all cancer types
clinical__nte	Specifies clinical information about an NTE (new tumor event)
clinical__rad	Specifies clinical information about radiation
clinical__rx	Specifies clinical information about drug treatment
clinical__shared	Specifies patient information properties shared between Clinical and Biospecimen Supplements of the same patient
clinical__shared_stage	Specifies clinical information about clinical stage
clinical__<tumor_tag>	Specifies clinical information about the specific tumor represented in <tumor_tag>, which corresponds to the value of *biospecimen__admin__disease_code* in the same file

For the TCGA project, the identifiers present in meta data derived from the Supplements are summarized in the following table:

Attribute	**Description**	**Example**
biospecimen__admin__file_uuid	UUID of the biospecimen file	A0B00C9D-5506-4606-893D-8BB1EEFB28B2
biospecimen__bio__bcr_analyte_barcode	Analyte barcode in biospecimen file	TCGA-AC-A2B8-01-11R
biospecimen__bio__bcr_portion_barcode	Portion barcode in biospecimen file	TCGA-AC-A2B8-01-11
biospecimen__bio__bcr_sample_barcode	Sample barcode in biospecimen file	TCGA-AC-A2B8-01
biospecimen__shared__bcr_patient_barcode	Patient barcode in the biospecimen file	TCGA-AC-A2B8
biospecimen__shared__patient_id	Code of the patient in biospecimen file	A2B8
clinical__admin__file_uuid	UUID of the clinical file	FCB31FE6-A2D6-4F30-A21C-37DF6009C4D7
clinical__admin__project_code	Code of the project in clinical file	TCGA
clinical__clin_shared__bcr_followup_barcode	Followup barcode in clinical file	TCGA-AC-A2B8-F43210
clinical__clin_shared__bcr_followup_uuid	Followup UUID in clinical file	E01D57EB-5162-4BCE-8AC8-D37DDBE74B3C
clinical__rad__bcr_radiation_barcode	Radiation barcode in clinical file	TCGA-AC-A2B8-R43215
clinical__rad__bcr_radiation_uuid	Radiation UUID in clinical file	DAB5FC3E-2668-4D3F-B2AD-9411CCACBF9C
clinical__rx__bcr_drug_barcode	Drug barcode in clinical file	TCGA-EK-A2RL-D58212
clinical__rx__bcr_drug_uuid	Drug UUID in clinical file	59e6c7ae-f010-4bc2-85b2-e95db499bc3a

The hierarchy of the TCGA IDs is depicted in the Aliquot Barcode figure:



Meta data in the TCGA project: from GDC API

Meta data retrieved through the GDC API are organized in subgroups that are listed in the following table. At their side we provide the link to the documentation of the specific entity. The documentation is particularly helpful to verify if meta data contained in each group are required or not. Each page contains a table describing the properties of such group and specifying which are mandatory.

ALIQUOT	aliquot documentation
ANALYSIS	analysis documentation
ANALYTE	analyte documentation
CASES	case documentation
CENTER	center documentation
DEMOGRAPHIC	demographic documentation
DIAGNOSIS	diagnosis documentation
EXPOSURES	exposure documentation
FILE	submittable_data_file or generated_data_file documentation
INPUT_FILES	submittable_data_file or generated_data_file documentation
PORTION	portion documentation
PROGRAM	program documentation
PROJECT	project documentation
SAMPLE	sample documentation
SLIDE	slide documentation
TISSUE SOURCE SITE	tissue_source_site documentation
TREATMENTS	treatment documentation

Each group contains one or multiple identifiers, which are unique for that entity. The identifiers present in meta data derived from the GDC API are listed in the following table, which contains example values coming from the file 001201ec-e31a-4887-b4d7-9b4139b7cdf2-ieq.bed.meta.

Meta data	Description	Example
gdc__aliquots__aliquot_id	ID of the aliquot	001201ec-e31a-4887-b4d7-9b4139b7cdf2
gdc__aliquots__submitter_id	ID of the submitter of the aliquot	TCGA-BH-A18S-01A-11R-A12C-13
gdc__analysis__analysis_id	ID of the workflow to obtain the file	47bcbe01-f506-40b3-bb67-8ed9cefe1273
gdc__analytes__analyte_id	ID of the analyte from which the aliquot is derived	a3e2a0f8-248b-4e0c-b2d1-6c623678bf57
gdc__case_id	ID of the case (patient) who donated the sample	433427a1-bacf-4381-91ba-5fec8a0953f9
gdc__center__center_id	ID of the center	6eba705a-0f00-5aa2-b1d0-04dbf62100cc
gdc__center__code	Code of the center	13
gdc__diagnoses__diagnosis_id	ID of the diagnosis information of the case	bc2ca8f2-6ee4-5ed6-b96b-849b2f1f5371
gdc__diagnoses__treatments__treatment_id	ID of the treatment information of the case	Not present
gdc__exposures__exposure_id	ID of the exposure information of the case	131af00c-4930-5fec-a972-f777734f0e7b
gdc__file_id	ID of the file retrieved from GDC	78a22de6-2501-4ba4-8b0a-e0c443a0ed20
gdc__portions__portion_id	ID of the portion from which the aliquot is derived	467ea50e-c200-44ac-ac56-76a703e94f17
gdc__program__name	Name of the program	TCGA
gdc__program__program_id	ID of the program	b80aa962-9650-5110-b3eb-bd087da808db
gdc__project__project_id	ID of the project, related to a specific cancer type	TCGA-BRCA
gdc__tissue_source_site__code	Code of the source site where the biological material was extracted	BH
gdc__tissue_source_site__tissue_source_site_id	ID of the source site where the biological material was extracted	ad5db77f-ce9a-53c8-b7ff-7944acf5c0c6
gdc__samples__sample_id	ID of the bio sample from which the aliquot is derived	ce3a4469-8d19-4661-9c48-1baf6e84f49c
gdc__slides__slide_id	ID of the slide from which the aliquot is derived	b3a7ecb9-c4bb-4f9d-8886-5884b6335567
gdc__submitter_id	ID of the submitter of the file	mirna_swap_dr11_841_MirnaExpressionaa1f4808-71ef-4bc0-b568-bfc88e17f98b_isoform_profiling

Notes:

1. With respect to original names retrieved from the GCD API, occasionally very long and

cumbersome, a simple renaming function has been applied, leaving unchanged the last subgroup and name of the attribute (last part of the fields) and ensuring that the simplified version allows nevertheless to uniquely identify the field. For example, *gdc__cases__samples__portions__analytes__aliquots__aliquot_id* has become *gdc__aliquots__aliquot_id*.

2. Many attribute-values were found as replicates between the meta data generated from the Supplements and those generated from GDC API. This happened especially in the case of identifiers. When two different meta data are always present with the same value in a same file, we preserve the naming from GDC API and discard the one from the Supplements. For example, between *clinical__clin_shared__ethnicity* and *gdc__demographic__ethnicity*, we preserve the second one, and between *biospecimen__bio__bcr_sample_uuid* and *gdc__samples__sample_id*, we also preserve the second one.
3. The meta data attribute *gdc__aliquots__aliquot_id* identifies a single experiment on a tissue aliquot of a patient and is used as primary identifier for the sequencing/array experiment. Multiple experiments (even of different type, e.g., about gene expressions, mutations, methylations, etc.) on the same biological sample (i.e., tissue aliquot) are identified and related together through the meta data attribute *gdc__samples__sample_id* which is the tissue identifier. Similarly, multiple experiments (regarding the same or different biological samples) of the same patient are identified and related together through the meta data attribute *gdc__case_id*, which is the identifier of the patient (i.e., case).
4. Other relevant meta data are described by the attributes: *gdc__disease_type* (i.e., the type of malignant disease, as categorized by the World Health Organization's (WHO) International Classification of Diseases for Oncology (ICD-O); *gdc__project__project_id* (i.e., the identifier of the Project, composed by dash concatenation of 'TCGA' and the tag of the tumor, such as 'BRCA', which leads to 'TCGA-BRCA'); *gdc__project__disease_type* (i.e., the full name for the project); *gdc__project__primary_site* (i.e., the general location of the malignant disease, as categorized by the ICD-O); *gdc_file_name* and *gdc__file_id*, uniquely identifying the origin aliquot file downloaded from GDC and transformed by OpenGDC.
5. The *gdc__diagnoses__days_to_birth* meta data represents the time interval from a person's date of birth to the date of initial pathologic diagnosis, represented as a calculated negative number of days[15].
6. The meanings of the alphanumeric values of the attribute *gdc__tissue_source_site__code* are available at https://gdc.cancer.gov/resources-tcga-users/tcga-code-tables/tissue-source-site-codes.
7. The meta data *gdc__file_id, gdc__file_name, gdc__file_size, gdc__md5sum,*

[15] https://docs.gdc.cancer.gov/Data_Dictionary/viewer/#?view=table-definition-view&id=demographic&anchor=days_to_birth

gdc__submitter_id, gdc__created_datetime, gdc__analysis__analysis_id, gdc__analysis__workflow_type of Gene Expression Quantification and Masked Somatic Mutation data provided in BED format have multiple values since such data combine data originally from three GDC files (FPKM, FPKM-UQ and counts) for Gene Expression Quantification and from four GDC files for Masked Somatic Mutation, each one obtained with a different Variant caller (MuSE, MuTect2, VarScan2 and SomaticSniper)[16]; values reported in each meta data are ordered accordingly to the here above reported order of the original files they refer to.

Meta data in the TCGA project: manually curated

All meta data attributes belonging to the group '`manually_curated`' are mandatory and always present in the .meta files generated in OpenGDC.

We consider the following ones (each one is reported with one output example value or all possible values, when possible):

1) **`manually_curated__data_format`**
`BED`

2) **`manually_curated__ exp_data_bed_url`**
`ftp://geco.deib.polimi.it/opengdc/bed/tcga/tcga-acc/copy_number_segment/c00b53a9-bb48-4841-974d-7087eacd5420-cns.bed`

3) **`manually_curated__exp_metadata_url`** `(required)`
`ftp://geco.deib.polimi.it/opengdc/bed/tcga/tcga-acc/clinical_and_biospecimen_supplements/c00b53a9-bb48-4841-974d-7087eacd5420-cns.meta`

4) **`manually_curated__genome_built`**
`GRCh38`

5) **`manually_curated__opengdc_download_date`**
`2018-10-11T17:12:59.000924+02:00`

6) **`manually_curated__opengdc_file_md5`**
`d3de15c5fb00f3132ae26c6567efef3d`

7) **`manually_curated__opengdc_file_size`**
`26173`

8) **`manually_curated__opengdc_id`**
`00b8b899-6191-4169-91bd-a507c326e44d-msm`

9) **`manually_curated__tissue_status`**

[16] https://docs.gdc.cancer.gov/Data/Bioinformatics_Pipelines/DNA_Seq_Variant_Calling_Pipeline/#masked-somatic-aggregation-workflow

```
        control | normal | tumoral | undefined
```

`manually_curated__data_format` describes the output format in which data files are produced by OpenGDC, starting from various input formats from GDC.

`manually_curated__exp_data_bed_url` and `manually_curated__exp_metadata_url` provide the OpenGDC FTP endpoints to download respectively data and meta data files corresponding to the described aliquot.

`manually_curated__genome_built` specifies the reference genome for alignment, as described in the reference paper[17].

`manually_curated__opengdc_download_date`, `manually_curated__opengdc_file_md5`, and `manually_curated__opengdc_file_size` reflect production properties of the genomic data file as it is output within the OpenGDC pipeline.

`manually_curated__opengdc_id` is the OpenGDC ID associated with the experimental output file; it is composed of the aliquot *gdc__aliquots__aliquot_id* and the acronym of the experiment type (data type), e.g., "00b8b899-6191-4169-91bd-a507c326e44d-msm" is related to the Masked Somatic Mutations data type.

Values of the attribute *`manually_curated__tissue_status`* are defined based on the value of the attribute *gdc__samples__sample_type_id* (whose value in range 01–09 and 40 indicates a tumor type, in range 10–14 indicates normal type, and 20 indicates control type; the comprehensive list of sample type codes is available at https://gdc.cancer.gov/resources-tcga-users/tcga-code-tables/sample-type-codes).

Correspondence with TCGA2BED meta data

We provide ID mappings to enable the comparison between data from TCGA2BED (http://bioinf.iasi.cnr.it/tcga2bed/, whose format is defined in http://bioinf.iasi.cnr.it/tcga2bed/data/TCGA2BED_format_definition.pdf) and OpenGDC.

OpenGDC	TCGA2BED	Description
biospecimen__bio__bcr_analyte_barcode	biospecimen_analyte__bcr_analyte_barcode	Analyte barcode in biospecimen file
biospecimen__bio__bcr_portion_barcode	biospecimen_portion__bcr_portion_barcode	Portion barcode in biospecimen file
biospecimen__bio__bcr_sample_barcode	biospecimen_sample__bcr_sample_barcode	Sample barcode in biospecimen file
biospecimen__shared__bcr_patient_barcode	biospecimen_tumor_sample__bcr_patient_barcode clinical_nte__bcr_patient_barcode	Patient barcode in the biospecimen file

[17] Jensen, Mark A., *et al*. The NCI Genomic Data Commons as an engine for precision medicine. *Blood,* 2017; 130(4): 453-459.

	clinical_patient__bcr_patient_barcode biospecimen_diagnostic_slides__bcr_patient_barcode	
clinical__clin_shared__bcr_followup_barcode	clinical_follow_up__bcr_followup_barcode	Followup barcode in clinical file
clinical__clin_shared__bcr_followup_uuid	clinical_follow_up__bcr_followup_uuid	Followup UUID in clinical file
clinical__rad__bcr_radiation_barcode	clinical_radiation__bcr_radiation_barcode	Radiation barcode in clinical file
clinical__rad__bcr_radiation_uuid	clinical_radiation__bcr_radiation_uuid	Radiation UUID in clinical file
gdc__aliquots__aliquot_id	**biospecimen_aliquot__bcr_aliquot_uuid**	documentation
gdc__aliquots__submitter_id	biospecimen_aliquot__bcr_aliquot_barcode	documentation
gdc__case_id	**biospecimen_aliquot__bcr_patient_uuid**	documentation
gdc__portions__portion_id	biospecimen_portion__bcr_portion_uuid	documentation
gdc__samples__pathology_report_uuid	biospecimen_sample__pathology_report_uuid	documentation
gdc__samples__sample_id	**biospecimen_sample__bcr_sample_uuid**	documentation
gdc__slides__slide_id	biospecimen_slide__bcr_slide_uuid	documentation

Three meta data (i.e., *gdc__case_id*, *gdc__samples__sample_id*, and *gdc__aliquots__aliquot_id*) have been highlighted in bold being the most important to distinguish respectively the patient, the biological sample and the aliquot (therefore the data file) of interest.

Additional output files

We also provide the following output files:

MD5 checksum files

One tab separated .txt ("*md5checksum.txt*") file for each experiment of each tumor with all the meta data and genomic data files, containing the name of the file and its md5 checksum.

Meta data dictionary file

One meta data dictionary tab-delimited file ("*meta_dictionary.txt*"), which contains all the possible values of any meta data attribute, for example:

biospecimen__bio__menopause_status
Pre (<6 months since LMP AND no prior bilateral ovariectomy AND not on estrogen replacement)
Peri (6-12 months since last menstrual period)
[Unknown]
Post (prior bilateral ovariectomy OR >12 mo since LMP with no prior hysterectomy)
CDE_ID:2957270
clinical__clin_shared__histologic_diagnosis_other
Mixed infiltrating lobular and grade 1 ductal carcinoma
MUCINOUS & PAPILLARY
CDE_ID:3124492
Lobular carcinoma with ductal features
ductal/lobular
IDC+ mucinous carcinoma
Ductal/Lobular
Infiltrating ductal & lobular
Infiltrating ductal and lobular carcinoma
ductal and lobular
Invasive ductal and lobular carcinoma
lobular/ductal
Mixed invasive ductal and invasive lobular
Lobular/Ductal
[Not Applicable]
Mixed diagnosis
with ductal and lobular phenotypes

When performing batch data format conversions, a meta data dictionary file is generated with all the converted data for each genomic experiment (data type) (e.g., DNA-seq, DNA-methylation, RNA-seq, miRNA-seq, and CNV) of each tumor.

Meta data information files

We output a comma separated values (CSV) file containing the occurrences of all the meta data attributes related to each experiment (data type) of each tumor ("*meta2disease_table.csv*").
Furthermore, we generate the following additional output files for each tumor:

- a CSV file containing the number of occurrences of each meta data attribute related to the tumor ("*meta2dataType_table.csv*")
- a CSV file containing a table with a list of all meta data attributes with all their possible values on the rows and the list of all available data types for the considered tumor on the columns; a generic cell of this table contains the number of occurrences of a specific attribute-value pair in a specific data type ("*meta_values2dataTypes_table.csv*")
- a tab separated values (TSV) file containing a list of all meta data attributes with all their possible values followed by the number of occurrences of each of these pairs (attribute-value) in all data types for the considered tumor ("*meta_values2sample_list.tsv*")

Experiment information files

We generate an additional output file for each subtype of all the genomic experiments (data types), regardless the related tumor and called "*exp_info.tsv*". It is a tab-delimited file that includes:

- number of aliquots;
- number of samples (tissues);
- number of patients.

Annotations files

Gene Expression Quantification
We provide the following additional annotation output files for the Gene Expression Quantification datasets:

(i) "*gene_expression_annotations.bed*", a bed file that contains the following fields for each gene in the considered genomic experiment:

1) chrom
2) start

3) end
4) strand
5) ensembl_gene_id
6) entrez_gene_id
7) gene_symbol
8) type

(ii) "*gene_expression_annotations.schema*", an xml file containing the structure and the fields of "*gene_expression_annotations.bed*"

(iii) "*gene_expression_annotations.bed.meta*", a metadata file containing following metadata related to the "*gene_expression_annotations.bed*" file:

1) **`annotation_type`**
   `gene`
2) **`assembly`**
   `GRCh38`
3) **`platform`**
   `Illumina`
4) **`external_annotations_source`**
   `HUGO Gene Nomenclature Committee (HGNC)`
5) **`external_annotations_source_url`**
   `http://rest.genenames.org`
6) **`gdc_annotations_source`**
   `GDC.h38 GENCODE v22 GTF annotation file`
7) **`gdc_annotations_source_url`**
   `https://api.gdc.cancer.gov/data/fe1750e4-fc2d-4a2c-ba21-5fc969a24f27`
8) **`name`**
   `gene regions for GDC Gene Expression Quantification`
9) **`original_provider`**
   `GENCODE`
10) **`provider`**
   `GDC`

DNA methylation

We provide the following additional annotation output files for the DNA methylation datasets:

(i) "*humanMethylation27_annotations.bed*", a bed file that contains the following fields for each methylated site in the considered genomic experiment:

1) chrom

2) start
3) end
4) strand
5) composite_element_ref
6) gene_symbol
7) entrez_gene_id
8) gene_type
9) ensembl_transcript_id
10) position_to_tss
11) all_gene_symbols
12) all_entrez_gene_ids
13) all_gene_types
14) all_ensembl_transcript_ids
15) all_positions_to_tss
16) cgi_coordinate
17) feature_type

(ii) "*humanMethylation27_annotations.schema*", an xml file containing the structure and the fields of "*humanMethylation27_annotations.bed*"

(iii) "*humanMethylation27_annotations.bed.meta*", a metadata file containing following metadata related to the "*humanMethylation27_annotations.bed*" file:

1) **annotation_type**
   `CpG site`
2) **assembly**
   `GRCh38`
3) **platform**
   `Illumina Human Methylation 27`
4) **external_annotations_source**
   `HUGO Gene Nomenclature Committee (HGNC)`
5) **external_annotations_source_url**
   `http://rest.genenames.org`
6) **gdc_annotations_source**
   `GDC.h38 GENCODE v22 GTF annotation file`
7) **gdc_annotations_source_url**
   `https://api.gdc.cancer.gov/data/fe1750e4-fc2d-4a2c-ba21-5fc969a24f27`
8) **name**
   `genomic coordinates related to the CpG site and gene`

regions associated to it

9) **original_provider**
   GENCODE
10) **provider**
    GDC

(iv) "*humanMethylation450_annotations.bed*", a bed file that contains the following fields for each methylated site in the considered genomic experiment:

1) chrom
2) start
3) end
4) strand
5) composite_element_ref
6) gene_symbol
7) entrez_gene_id
8) gene_type
9) ensembl_transcript_id
10) position_to_tss
11) all_gene_symbols
12) all_entrez_gene_ids
13) all_gene_types
14) all_ensembl_transcript_ids
15) all_positions_to_tss
16) cgi_coordinate
17) feature_type

(v) "*humanMethylation450_annotations.schema*", an xml file containing the structure and the fields of "*humanMethylation450_annotations.bed*"

(vi) "*humanMethylation450_annotations.bed.meta*", a metadata file containing following metadata related to the "*humanMethylation27_annotations.bed*" file:

1) **annotation_type**
   CpG site
2) **assembly**
   GRCh38
3) **platform**
   Illumina Human Methylation 450
4) **external_annotations_source**
   HUGO Gene Nomenclature Committee (HGNC)
5) **external_annotations_source_url**
   http://rest.genenames.org

6) **`gdc_annotations_source`**
   `GDC.h38 GENCODE v22 GTF annotation file`

7) **`gdc_annotations_source_url`**
   `https://api.gdc.cancer.gov/data/fe1750e4-fc2d-4a2c-ba21-5fc969a24f27`

8) **`name`**
   `genomic coordinates related to the CpG site and gene regions associated to it`

9) **`original_provider`**
   `GENCODE`

10) **`provider`**
   `GDC`

Summary table of the additional output files

Meta data	*meta_dictionary.txt*
Gene Expression Quantification	*gene_expression_annotations.bed* *gene_expression_annotations.bed.meta* *gene_expression_annotations.schema*
DNA methylation	*humanMethylation27_annotations.bed* *humanMethylation27_annotations.bed.meta* *humanMethylation27_annotations.schema* *humanMethylation450_annotations.bed* *humanMethylation450_annotations.bed.meta* *humanMethylation450_annotations.schema*
For each data type	*exp_info.tsv* *md5checksum.txt*
General	*meta2dataType_table.csv* *meta2disease_table.csv* *meta_values2dataTypes_table.csv* *meta_values2sample_list.tsv*

Additional data file formats

Besides the BED format, to ensure maximum usage, we also support the set of additional data file formats following specified.

CSV format

The standard Comma Separated Values (CSV) file format defines the structure and content of the genomic data files as equal to the ones of the BED format, but a comma (instead of a tabulator) is used to separate the different fields.
The structure of the meta data files is the same as for the BED format.

XML format

The standard eXtended Markup Language (XML) file format specifies the content of the genomic data files as equal to the one of the BED format, but the file structure is designed according to the XML style. In particular, we define one genomic data XML file for each aliquot and experiment type; the content of this file starts with the XML heading line
`<?xml version="1.0" encoding="UTF-8"?>`
and with the root tag called `<aliquot>`.
Then, for each genomic measure (row of the input data file) we define a `<data>` tag containing the measured attributes and their values as sub-tags.
In the following, we provide an example of XML file of DNA methylation:

```
<?xml version="1.0" encoding="UTF-8"?>
<aliquot>
    <data>
        <chr>chr17</chr>
        <start>62503072</start>
        <stop>62503072</stop>
        <strand>+</strand>
        <composite_element_ref>cg00003784</composite_element_ref>
        <beta_value>0.0286291327274318</beta_value>
        <gene_symbol>CEP95</gene_symbol>
    </data>
    <data>
        <chr>chr19</chr>
        <start>17336525</start>
        <stop>17336525</stop>
        <strand>+</strand>
        <composite_element_ref>cg00003818</composite_element_ref>
        <beta_value>null</beta_value>
        <gene_symbol>OCEL1</gene_symbol>
    </data>
    …
</aliquot>
```

The structure of the meta data files is the same as for the BED format.

JSON format

The standard JavaScript Object Notation (JSON) format specifies the content of the genomic data files as equal to the one of the BED format, but the file structure is designed according to the JSON style. In particular, we define one genomic data JSON file for each aliquot and experiment type; the content of this file starts with the root tag called `“aliquot”`.

Then, for each genomic measure (row of the input data file) we define a `“data”` tag containing the measured attributes and their values as sub-tags.

In the following, we provide an example of JSON file of DNA methylation:

```
{
    "aliquot": {
        "data": [
            {
                "chr": "chr17",
                "start": "62503072",
                "stop": "62503072",
                "strand": "+",
                "composite_element_ref": "cg00003784",
                "beta_value": "0.0286291327274318",
                "gene_symbol": "CEP95"
            },
            {
                "chr": "chr19",
                "start": "17336525",
                "stop": "17336525",
                "strand": "+",
                "composite_element_ref": "cg00003818",
                "beta_value": "null",
                "gene_symbol": "OCEL1"
            },
….
}
```

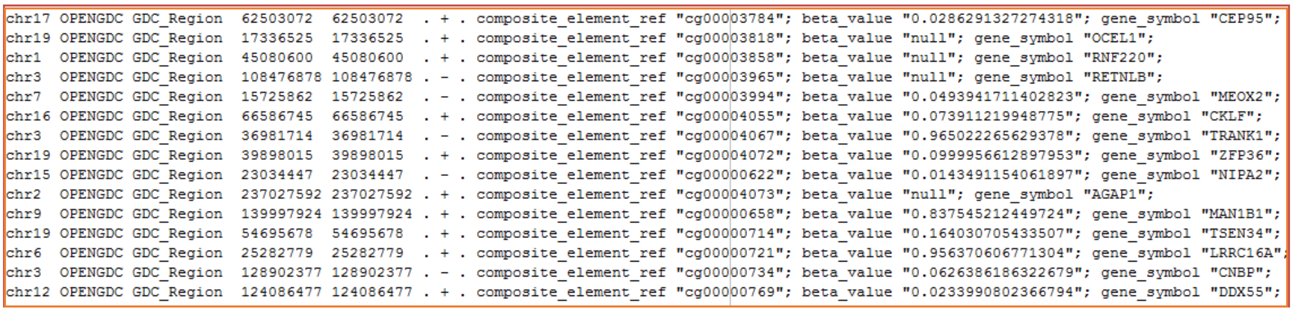
The structure of the meta data files is the same as for the BED format.

GTF format

The bioinformatics standard Gene Transfer Format (GTF) specifies the content of the genomic data files as equal to the one of the BED format, but the file structure is designed according to the GTF style. In particular, we define one genomic data GTF file for each aliquot and experiment type.
The nine tab separated GTF fields are[18]:

1. **seqname** - the name of the sequence; it must be a chromosome or scaffold (in our case, the chromosome).
2. **source** - the program that generated this feature (in our case, OpenGDC)
3. **feature** - the name of this type of feature; some examples of standard feature types are "CDS", "start_codon", "stop_codon" and "exon" (in our case, "GDC_Region").
4. **start** - the starting position of the feature in the sequence; the first base is numbered 1.
5. **end** - the ending position of the feature in the sequence (inclusive).
6. **score** - a score between 0 and 1000. In UCSC Genome Browser, if the track line *useScore* attribute is set to 1 for this annotation data set, the *score* value determines the level of gray in which this feature is displayed (higher numbers = darker gray). If there is no score value, "." is entered.
7. **strand** - valid entries include '+', '-', or '.' (for do not know/do not care).
8. **frame** - if the feature is a coding exon, *frame* should be a number between 0 and 2 that represents the reading frame of the first base; if the feature is not a coding exon, the value should be '.'.
9. **group** - a list of attributes; each attribute consists of a name-value pair (in our case, we include the fields of the genomic data file and their values, e.g., composite_element_ref "cg00003784"; beta_value "0.0286291327274318"; gene_symbol "CEP95"). Attributes must end with a semi-colon and be separated from any following attribute by exactly one space.

In the following, we provide an example of GTF file of DNA methylation:



```
chr17 OPENGDC GDC_Region  62503072  62503072  . + . composite_element_ref "cg00003784"; beta_value "0.0286291327274318"; gene_symbol "CEP95";
chr19 OPENGDC GDC_Region  17336525  17336525  . + . composite_element_ref "cg00003818"; beta_value "null"; gene_symbol "OCEL1";
chr1  OPENGDC GDC_Region  45080600  45080600  . + . composite_element_ref "cg00003858"; beta_value "null"; gene_symbol "RNF220";
chr3  OPENGDC GDC_Region  108476878 108476878 . - . composite_element_ref "cg00003965"; beta_value "null"; gene_symbol "RETNLB";
chr7  OPENGDC GDC_Region  15725862  15725862  . - . composite_element_ref "cg00003994"; beta_value "0.0493941711402823"; gene_symbol "MEOX2";
chr16 OPENGDC GDC_Region  66586745  66586745  . + . composite_element_ref "cg00004055"; beta_value "0.073911219948775"; gene_symbol "CKLF";
chr3  OPENGDC GDC_Region  36981714  36981714  . - . composite_element_ref "cg00004067"; beta_value "0.965022265629378"; gene_symbol "TRANK1";
chr19 OPENGDC GDC_Region  39898015  39898015  . + . composite_element_ref "cg00004072"; beta_value "0.0999956612897953"; gene_symbol "ZFP36";
chr15 OPENGDC GDC_Region  23034447  23034447  . - . composite_element_ref "cg00000622"; beta_value "0.0143491154061897"; gene_symbol "NIPA2";
chr2  OPENGDC GDC_Region  237027592 237027592 . + . composite_element_ref "cg00004073"; beta_value "null"; gene_symbol "AGAP1";
chr9  OPENGDC GDC_Region  139997924 139997924 . + . composite_element_ref "cg00000658"; beta_value "0.837545212449724"; gene_symbol "MAN1B1";
chr19 OPENGDC GDC_Region  54695678  54695678  . + . composite_element_ref "cg00000714"; beta_value "0.164030705433507"; gene_symbol "TSEN34";
chr6  OPENGDC GDC_Region  25282779  25282779  . + . composite_element_ref "cg00000721"; beta_value "0.956370606771304"; gene_symbol "LRRC16A";
chr3  OPENGDC GDC_Region  128902377 128902377 . - . composite_element_ref "cg00000734"; beta_value "0.0626386186322679"; gene_symbol "CNBP";
chr12 OPENGDC GDC_Region  124086477 124086477 . + . composite_element_ref "cg00000769"; beta_value "0.0233990802366794"; gene_symbol "DDX55";
```

The structure of the meta data files is the same as for the BED format.

[18] https://genome.ucsc.edu/FAQ/FAQformat#format4