The UCSC Xena Platform for cancer genomics data visualization and interpretation

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Abstract

UCSC Xena is a web-based visual integration and exploration tool for multi-omic data and associated clinical and phenotypic annotations. The platform consists of a web-based Xena Browser and turn-key Xena Hubs. Xena showcases seminal cancer genomics datasets from TCGA, Pan-Cancer Atlas, PCAWG, ICGC, and the GDC; a total of more than 1500 datasets across 50 cancer types. We support virtually any functional genomics data modality, including SNVs, INDELs, large structural variants, CNV, gene- and other types of expression, DNA methylation, clinical and phenotypic annotations. A researcher can host their own data securely via a private hub on a laptop or behind a firewall, with visual and analytical integration occurring only within the Xena Browser. Browser features include our high performance Visual Spreadsheet, dynamic Kaplan-Meier survival analysis, powerful filtering and subgrouping, statistical analyses, genomic signatures, bookmarks, box plots, and scatter plots.

Introduction

The genomics data landscape has transitioned into the 'Big Data' realm. In fact, by 2025, the total amount of genomics data is expected to match the three other major producers of large data (astronomy, YouTube, and Twitter) combined (Stephens 2015). Recent technological advances, including high-throughput, whole-genome, and single-cell sequencing, has been in part responsible for the expanding volume of data (Mardis 2008). This growth has led the need for ever more powerful, but still interactive, visualization and analysis tools to extract knowledge from these large datasets (Schroeder 2015).

Adding to the challenge is the growing data complexity, including the expanding variety of data modalities. For example, in addition to the relatively common gene expression and somatic mutation datasets, we are starting to see DNA methylation datasets as assayed by whole genome bisulfite sequencing (Zhou 2018) and nucleosome

occupancy assayed by ATAC-seq. Each of these modalities provides a unique window into the genome; Integrating across them is challenging but necessary to gain a more in-depth understanding of a tumor's genomic events.

The highly distributed nature of this data also poses a significant challenge. Most investigators generate relatively small-scale datasets which are only used by a few researchers. In contrast, organized large consortia, such as TCGA (The Cancer Genome Atlas) (Chin 2011, Chin 2011) and the GDC (Genomic Data Commons) (Grossman 2016), generate or host large, high-value datasets that are used by researchers all over the world. Despite data sharing efforts, these two sources of data tend to be “siloed” and cannot be easily connected.

The UCSC Xena system was developed in response to these concurrent data challenges of increasing volume, expanding modalities, and wide physical distribution. UCSC Xena enables cancer researchers of all computational backgrounds to explore large diverse datasets, both public as well as their own, no matter where the data is located (Cieślik 2018, Langmead 2018). Xena hosts datasets from landmark cancer genomics resources including TCGA, ICGC (International Cancer Genome Consortium) (The International Cancer Genome Consortium 2010), and the GDC. The system easily supports tens of thousands of samples and has been tested up to as many as a million cells. The simple and flexible architecture supports a variety of common and uncommon genomic and clinical data types. Xena's unique visualizations integrate gene-centric and genomic-coordinate-centric views across multiple data modalities, providing a deep, comprehensive view of genomic events within a cohort of tumors.

Results

UCSC Xena (http://xena.ucsc.edu) is a visual integration and exploration tool for multi-omic data. The Xena platform has two components: the web-based Xena Browser and the back-end Xena Hubs (Figure 1). The Xena Browser empowers biologists to explore data across multiple Xena Hubs using a variety of visualizations and analyses. The back-end Xena Hubs store genomics data and are configured to be public or private and can be installed on laptops, public servers, behind a firewall, or in the cloud (Figure 1). Xena Browser simultaneously connects to any number of Xena Hubs, with integration occurring in the browser, allowing data to be distributed across multiple Xena Hubs.

This architecture with a decoupled front-end Xena Browser and back-end Xena Hubs has several advantages. First, researchers can easily view their own private data by installing their own Xena Hub. Xena Hubs are lightweight compared to a full-fledged

application and install easily on most computers. Second, users can use the same platform to view both public and private data together. Many tools aimed at visualizing private data require users to download data from large public datasets to view on the same platform. Xena integrates data across multiple hubs, allowing users to view data from separate hubs as a coherent data resource while keeping private data secure. Third, the Xena platform scales easily. As more datasets are generated, more Xena Hubs are added to the network, effectively growing with expanding genomics resources.

Supported data types and public resources

Cancer genomics research is increasingly multi-omic. Today, studies commonly collect data on somatic mutations, copy number and gene expression, with other data types being relatively rare. However, as genomics technology advances, we expect these rarer data types to increase in frequency and new data types to be produced. With this in mind we designed Xena to be able to load any tabular or matrix formatted data, giving us exceptional flexibility in the data types we can visualize. Current supported data modalities include somatic and germline SNPs, INDELs, large structural variants, copy number variation, gene-, transcript-, exon-, protein-expression, DNA methylation, ATAC-seq peak signals, phenotype, clinical data, and sample annotations.

UCSC Xena provides interactive online visualization of seminal cancer genomics datasets. To showcase these data resources, we deploy seven public Xena Hubs. Together, they host 1557 datasets from more than 50 cancer types, including the latest from TCGA (Hoadley 2018), ICGC, PCAWG (Pan-Cancer Analysis of Whole Genomes) (Campbell 2017), and the GDC (Table 1). Our TCGA Hub hosts data from TCGA, the most comprehensive cancer genomics dataset to-date, with a full set of data modalities for 12,000+ samples across 30+ cancer types. The Xena TCGA Hub hosts all public-tier TCGA derived datasets including somatic mutation, copy number variation, gene and exon expression, and more. Our Pan-cancer Altas Hub hosts data from the latest TCGA project, the Pan-Cancer Atlas, which conducted an integrative molecular analysis of the all tumors in TCGA. In addition a uniform analysis, there are also highly curated datasets such as molecular subtypes and multiple survival endpoints. Our ICGC Hub hosts data from the ICGC project, a global effort to create a comprehensive description of the genomic, transcriptomic and epigenomic changes in 50 different tumor types. Our PCAWG Hub supports PCAWG, an analysis of 2,600 ICGC whole-cancer genomes and their matching normal tissues across 39 distinct tumour types (Campbell 2017). Its datasets include somatic mutation data from the whole genome, large structural variants, RNAseq-based data analysis, mutational signatures, curated histology, and more. Our GDC Hub hosts data from GDC, where the TCGA and TARGET data was uniformly recomputed using state-of-art pipelines and the latest human genome assembly, hg38. In addition to these well-known resources, we also host results from

the UCSC RNAseq recompute Toil pipeline, a uniformly re-aligned and re-called gene and transcript expression dataset for all TCGA, TARGET and GTEx samples (Vivian 2017). This dataset allows users to compare gene and transcript expression of TCGA 'tumor' samples to corresponding GTEx 'normal' samples. Lastly, the UCSC Public Hub has data we curated from various literature publications such as CCLE (Cancer Cell Line Encyclopedia, Barretina 2012). Xena Hubs load only the derived datasets, leaving the raw sequencing data at their respective locations. Xena complements each of seminal resources by providing powerful interactive visualizations for these data. All public Xena Hubs (https://xenabrowser.net/hub/) are open access, with no account or login required.

In addition to visualization, these public data hubs support data download en bulk for downstream analyses. We also offer programmatic access to slices of data through the Xena python package (https://github.com/ucscXena/xenaPython), which can be used independently or in a Jupyter Notebook to access any of the public Xena Hubs.

Turn-key Xena Hub

Xena Hubs are designed to be turn-key, allowing users who may not be computationally savvy to install and run a Xena Hub on their personal computer. Hubs are easily initiated using a point-and-click interface or through the command line. Xena Hubs run on most operating systems, including Windows, MAC and Linux. A dockerized version of the Xena Hub can be used as part of an automated workflow pipeline to visualize computational results.

Xena Hubs can be configured to be private or public. Hubs running on a laptop are private as they only allow connections from the users' own Xena Browser. Users can use a laptop hub to quickly and securely view their own data. Xena Hubs started in the cloud or on a server can be kept private by using a firewall. This enables easy sharing of private data within a lab, institution, or as part of a larger collaboration. They also can be configured to be public, making the data accessible to the larger community after investigation and publication.

An example of a public hub hosted by an institution is the Treehouse Hub, which was built and deployed by the Treehouse project (https://treehousegenomics.soe.ucsc.edu). It hosts RNAseq gene expression data of TCGA and TARGET samples combined with Treehouse''s pediatric cancer samples. This data is used to facilitate interpretation of a pediatric sample in the context of a large pan-cancer cohort since all samples were processed by the same bioinformatics pipeline. Since the data hub is setup separately, Treehouse has complete control over the data and data access. They have configured

their hub to be public, giving access to anyone who uses the Xena Browser or the Xena APIs.

Performance is critical for an interactive visualization tool, especially on the web. As the sample size for genomic experiments steadily increases, this has become a challenge for many tools. Knowing this, we optimized Xena Hubs to support data queries on tens of thousands of samples and more, delivering slices of genomic and clinical data within a few seconds.

Xena Browser

The Xena Browser is an online visual exploration tool for data in one or more Xena Hubs. Our visualizations and analyses include the Xena Visual Spreadsheet, survival analysis, scatter plots, bar graphs, statistical tests and genomic signatures. Researchers can dynamically generate and compare subgroups using Xena's sophisticated filtering and searching. In addition to the Brower's own views, we connect with a variety of complementary visualization tools, including the UCSC Genome Browser. The Xena Browser supports dynamic genomic signatures, allowing users to explore the relationship between a score and other -omic and clinical/phenotype data. Its shareable bookmarks and high resolution pdfs enhance collaborations and results dissemination. We support modern web browsers such as Chrome, Firefox or Safari.

Visual Spreadsheet

Integration across diverse data modalities provides a more biologically complete understanding of a genomic event. It is essential to view different types of data, such as gene expression, copy number, and mutations, on genes or genomic regions side-by-side. We designed our primary visualization, the Xena Visual Spreadsheet, to facilitate this integration. Analogous to an office spreadsheet application, it is a visual representation of a data grid where each column is a slice of genomic or phenotypic data (e.g. gene expression or age), and each row is a single entity (e.g. a bulk tumor sample, cell line, or single cells) (Figure 2). Rows of these entities are sorted according to the genomics data being displayed. Researchers can easily and rapidly reorder the Visual Spreadsheet, leading to a variety of views in real time and enabling the discovery of patterns among genomic and phenotype parameters. Xena's Visual Spreadsheet excels at integrating diverse sets of genomics data over a cohort of samples as well as nimbly re-sorting columns to reveal relationships, even when the data are hosted across multiple data hubs.

Xena's Visual Spreadsheet displays genomic data in both gene-centric and coordinate-centric views. Gene-centric views show data mapped to a gene or portion of a gene,

such as exons, transcripts, or specific CpG islands, and can display either exonic regions only or include data mapped to introns. Coordinate-centric views show data along the genomic coordinate, displaying copy number variation, simple mutations, structural variants, DNA methylation, and more (Supplemental Figure 1). Genomic intervals, from base level up to an entire chromosome, can be viewed through dynamic zooming into a region of interest or by entering specific coordinates. Both gene- and coordinate-centric views support coding and non-coding regions (Supplemental Figure 2). Links to the UCSC Genome Browser give genomic context to any gene or chromosome region. In addition to these various genomics views, we also visualize phenotype and clinical data such as age, gender, expression signatures, cell types, and subtype classifications. These phenotypic data are crucial to enable users to go beyond the genomic-only discoveries. All these different columns and views can be placed side-by-side in a single Xena Visual Spreadsheet.

The power of the Visual Spreadsheet is its data integration. Integration across different data modalities, such as gene expression, copy number variation, and DNA methylation, gives users a more comprehensive view of a genomic event in a tumor sample. For example, Xena's Visual Spreadsheet can help elucidate if higher expression for a gene is driven by copy number amplification or by promoter hypomethylation. Integration across gene- and coordinate-centric views helps users examine these events in different genomic contexts. For example, Xena's Visual Spreadsheet can help elucidate if a gene amplification is part of chromosomal arm duplication or a focal amplification. Integration across genomic and clinical data gives users the ability to make connections between genomic patterns and clinically relevant phenotypes such as subtype and survival. For example, Xena's Visual Spreadsheet can help elucidate if a mutation in a gene is enriched in a specific cancer type or subtypes.. These diverse integrations help researchers harness the power of comprehensive genomics studies, driving discovery and a deeper understanding of cancer biology.

More browser visualizations and functionalities

In addition to the Visual Spreadsheet, Xena has several other powerful views and analyses. Our Kaplan-Meier analysis allows users to statistically assess survival stratification by any genomic or phenotypic data (Figure 3). Bar charts, box plots and scatter plots, all with statistical tests automatically computed (chi-squared, t-test, or ANOVA as appropriate), provide additional insights into the data (Supplemental Figure 3). The Transcript View enables comparison of transcript-level expression between two groups of samples, such as TCGA 'tumor' vs. GTEx 'normal', for all the transcripts of a gene (Figure 4). We also provide context-dependent links to complementary visualizations such as the Tumor Map (https://tumormap.ucsc.edu) (Newton 2017) and

MuPIT in CRAVAT (http://mupit.icm.jhu.edu/) (Niknafs 2013), enabling users to easily see a genomic pattern from a different perspective.

Gene-expression signatures are developed to differentiate distinct subtypes of tumors, identify important cellular responses to their environment, and predict clinical outcomes in cancer (Sotiriou 2009). Xena's genomic signature functionality allows users to enter a signature as a weighted sum of a marker gene set, a form commonly seen in publications, and dynamically build a new spreadsheet column of the resulting scores. This functionality allows researchers to test existing signatures or build new ones, allowing the comparison of a signature score with other genomic and phenotypic data.

Our powerful text-based search allows users to dynamically highlight, filter, and group samples (Figure 5). Researchers can search the data on the screen similar to the 'find' functionality in Microsoft Word. Samples are matched and highlighted in real-time as the user types. Researchers can filter, focusing the visualization to their samples of interest, or dynamically build a new two-group column, where samples are marked as 'true' or 'false', depending if they meet the researcher's search criteria. The new two-group column behaves like any other column and can be used in a Kaplan-Meier analysis, box plot, or other statistical analyses to compare the two groups of samples. This is a powerful way to dynamically construct two subpopulations for comparison and analysis.

Being able to share and distribute biological insights is crucial, especially in this era of collaborative genomics. Xena's bookmark functionality enables the sharing of live views. With a single click, users can generate a URL of their current view, which will take researchers back to the live browser session. The URL can be shared with colleagues or included in presentations. If a view contains data from a non-public Xena Hub, we allow users to download the current visualization state as a file. This file can then be appropriately shared, and imported into the Xena Browser to recreate the live view. By giving users a file instead of a URL, we ensure that user's private data is secure. In addition to bookmarks, researchers can generate a high resolution PDF figure of their current visualization for reports and publications.

To assist researchers in building a Visual Spreadsheet, we developed a short three-step guided wizard. This ensures that even new users who are unfamiliar with Xena can build basic visualizations. We also provide links to live examples that showcase useful and scientifically interesting visualizations, highlighting the power of Xena. We support our users by developing training videos, online and in-person workshops, and through help documentation. We keep users up-to-date on new features and datasets through social media, mailing lists and monthly newsletter.

Discussion

UCSC Xena is a tool for cancer researchers to explore, visualize, and analyze functional genomics data. We host many large public datasets, such as TCGA, Pan-Cancer Atlas, PCAWG, GDC, and ICGC, helping to make these powerful resources accessible to investigators. The Visual Spreadsheet, sophisticated filtering and subgrouping, and Kaplan-Meier analysis enable researchers of all computational backgrounds to investigate complex genomics datasets. We support virtually all data modalities including mutations, copy number, expression, phenotype and clinical data as well as rare data types such as non-coding mutations, large structural variants, DNA methylation, and ATAC-seq peak signals. Integration across different data modalities and visualizations, as well as between genomic and clinical data yield insightful views into cancer biology.

UCSC Xena complements existing tools including the cBio Portal (http://www.cbioportal.org/, Cerami 2012), ICGC Portal (https://dcc.icgc.org/, Zhang 2011), GDC Portal (https://portal.gdc.cancer.gov/, Jensen 2017), IGV (http://software.broadinstitute.org/software/igv/, Thorvaldsdóttir 2013), and St. Jude Cloud (https://stjude.cloud/, Ma 2018), by focusing on providing a platform to visualize data across multiple hubs simultaneously. This enables biologists to easily view their own data as well as consortium data while still maintaining data privacy. Additionally, Xena focuses on simultaneous, integrative visualization of multi-omics datasets across different genomic contexts, including gene, genomic element, or any genomic region for both coding and non-coding part of the genome. Finally, Xena is built for performance. It can easily visualize of tens of thousands of samples in a few seconds and has been tested up to a million cells. With single-cell technology, datasets will become several orders of magnitude larger than traditional bulk tumor samples. Xena is well-positioned to rise to the challenge.

While it is widely recognized that data sharing is key to advancing cancer research, how it is shared can impact the ease of data access. UCSC Xena is a designed for cancer researchers both with and without computational expertise to share and access data. Users without a strong computational background can explore their own data by installing a Xena Hub on their personal computer using our point-and-click interface. Bioinformaticians can install a private or public Xena Hub on a server or in the cloud or as part of an analysis pipeline, making the generated data available in a user-friendly manner that requires little extra effort. Data sharing has, and will continue to, advance cancer biology and Xena is part of the technological ecosystem that helps support this.

UCSC Xena is a scalable solution to the rapidly expanding and decentralized cancer genomics data. Xena's architecture, with it's detached data hubs and web-browser-based visualization, allows new projects to easily add their data to the growing compendium that we support. Additionally, by maintaining a flexible input formats, we support many different data modalities, both now and in future. In this age of expanding data resources, Xena's design supports the ongoing needs of the cancer research community.

Xena excels at viewing cohorts of samples, cells, or cell lines and showing trends across those entities, whether they be human or a model organism. While we have focused on cancer genomics, the platform is general enough to host any functional genomics data. We hope to expand Xena to continue to help serve the genomics needs of the biomedical community.

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Methods

Public Xena Hubs

We download functional genomics data from each respective source: GDC data portal (https://portal.gdc.cancer.gov/repository) for the GDC Hub, GDC legacy archive (https://portal.gdc.cancer.gov/legacy-archive) for the TCGA Hub, ICGC data portal (https://dcc.icgc.org/) for the ICGC Hub, Synapse TCGA Pancan Atlas Data project (https://www.synapse.org/#!Synapse:syn3241074/wiki/194741) for the Pan-Cancer Atlas Hub, Synapse ICGC-TCGA Whole Genome Pan-Cancer Analysis project (https://www.synapse.org/#!Synapse:syn2351328/wiki/62351) for PCAWG hub, and various publications for data hosted on the UCSC Public Hub and UCSC RNAseq Recompute Toil Hub. The GDC and ICGC Hubs are updated periodically.

The downloaded data were wrangled into a generic tabular or matrix format, and loaded into the corresponding Xena Hubs. Specific wrangling steps, including any normalization, is listed for each dataset in the Xena Browser dataset pages (https://xenabrowser.net/datapages/). The wrangled data is available for bulk download from the dataset pages. Hundreds of gigabytes are typically downloaded each month from our hubs. For example, 797.25 GB of compressed data were downloaded in the month of July 2018.

We deploy all public-facing Xena Hubs in the Amazon Web Services (AWS) cloud-computing environment. Each hub is built using an AWS elastic load balancer connected to two EC2 r4.4xlarge servers. This architecture ensures fast performance even when user queries are highly concurrent. Response rates in this environment are, on average, 541 ms with 50 users making concurrent requests (tested using the TCGA Breast Cancer cohort data). The Treehouse Hub was separately built and deployed by the Treehouse project.

Xena Hub

The Xena Hub is a JVM-based application, written in Clojure, that serves functional genomic data over HTTP. It exposes a relational query API for data slicing and metadata. We decided to use a query language instead of REST for our APIs because it allowed us to decouple the client and server. To support interactive visualization, REST APIs would have to be denormalized for performance (e.g. by joining related objects, and projecting the result). This would require a tight coupling between the REST endpoints and particular views, and therefore frequent server redeployment to match browser client updates. Using REST becomes impractical because all the hubs in the Xena System will need to be updated including the ones people installed on their laptops or servers. In contrast to REST APIs, a query language allows us to fetch exactly the data we need, and only the data we need, for quickly evolving visualizations and data shapes, without redeployment of the hubs. This is similar in motivation to Facebook's GraphQL, and Netflix's Falcor, but predates them.

Internally, Xena Hubs use the H2 database for storage. Data is stored in opaque blocks in a column orientation, which allows fast retrieval of a field for all samples of a dataset, or a subset of samples. A hub can be installed either via the command line or via the point-and-click install4j graphical user interface.

Xena Browser

The Xena Browser is a javascript application to visualize and analyze functional genomics data stored in one or more Xena Hubs. The primary technologies are React,

the 2D canvas API, and RxJS. Babel is used for es6 support, and webpack for the build. The application architecture is an asynchronous model similar to redux-observable (https://redux-observable.js.org/), with semantic actions that update application state, and action side-effects creating Rx streams that will dispatch later actions. The redux (https://redux.js.org/), or Om (https://github.com/omcljs/om), pattern of immutable, single-atom state makes it simple to keep multiple views in sync, and provides “time travel” debugging during development.

We prefer the canvas API to SVG libraries such as D3, because it performs better at large data scales. With the advances in javascript JIT compilers, we find that optimized loops over canvas pixel buffers out-perform geometric drawing primitives, such as *rect()*, and *stroke()*, when rendering dense views of large data.

The jsverify property-based testing library (http://jsverify.github.io/) is used for unit and integration testing. Property-based, or "generative" testing is similar to fuzzing -- generating random test cases, and asserting invariants over the results -- but on failure, attempts to find a minimal failing test case. This usually results in more tractable failure cases. Property-based testing allows us to test a much larger portion of the input space than conventional "known-answer" unit tests, and frequently identifies failure cases that we would never think to test.

All of our code is open source and available for reuse under and Apache 2.0 license (https://github.com/ucscXena). We also have contributed two javascript modules to BioJS (Gómez 2013), including a Kaplan-Meier module (https://github.com/ucscXena/kaplan-meier) to compute Kaplan-Meier statistics, and a static-interval-tree library (https://github.com/ucscXena/static-interval-tree) to effectively find overlapping intervals in one dimension.

Figures and Tables

Figure 1

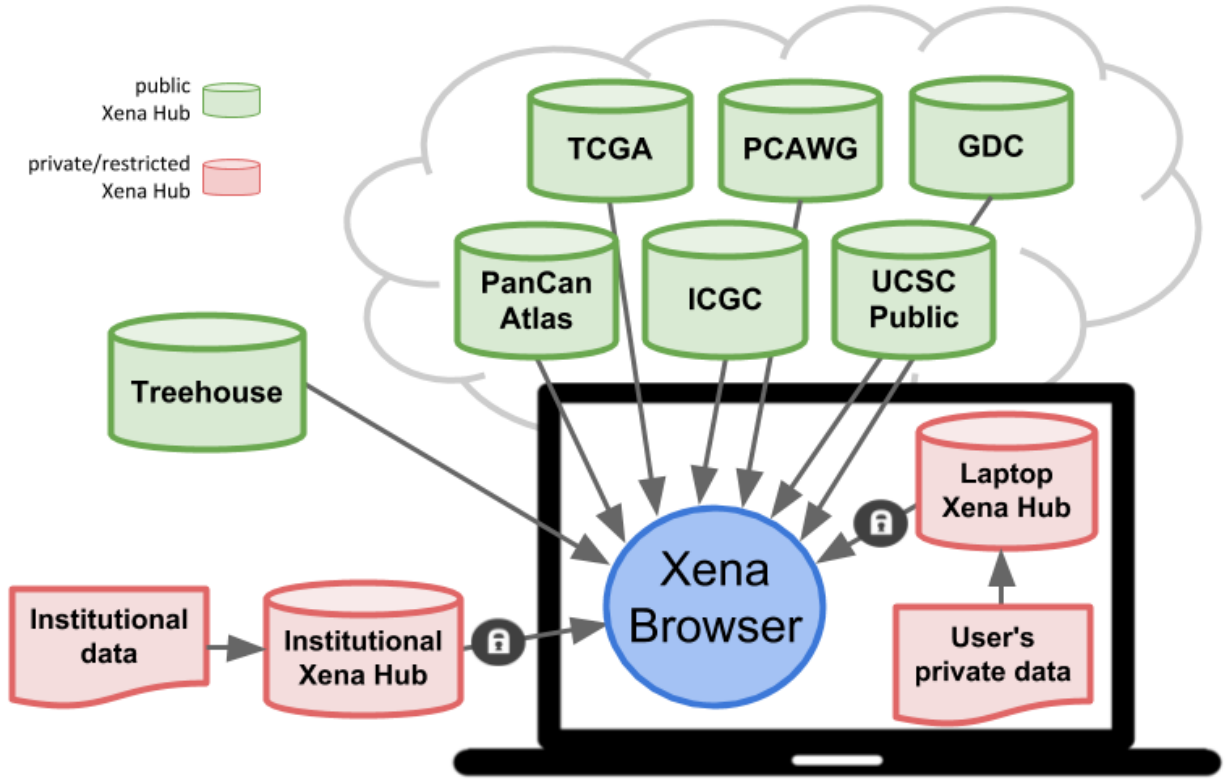


Figure 1. Diagram of the UCSC Xena platform architecture. Multiple Xena Hubs (each shown as a database icon) are connected to the Xena Browser simultaneously. Public hubs are in green and and private hubs in red. In this example, private data from an independent research collaboration (in red) is loaded into their own private Xena Hubs on their servers. Similarly, user's private data (in red) is loaded into a private Xena Hub on a researcher's computer. Data integration occurs within the Xena Browser on the user's computer. The lock icon indicates that only authorized users have access to the private Xena Hubs. Data only flows from hub to browser. This design achieves data integration across both public and private resources while maintaining each hub's data confidentiality.

Figure 2

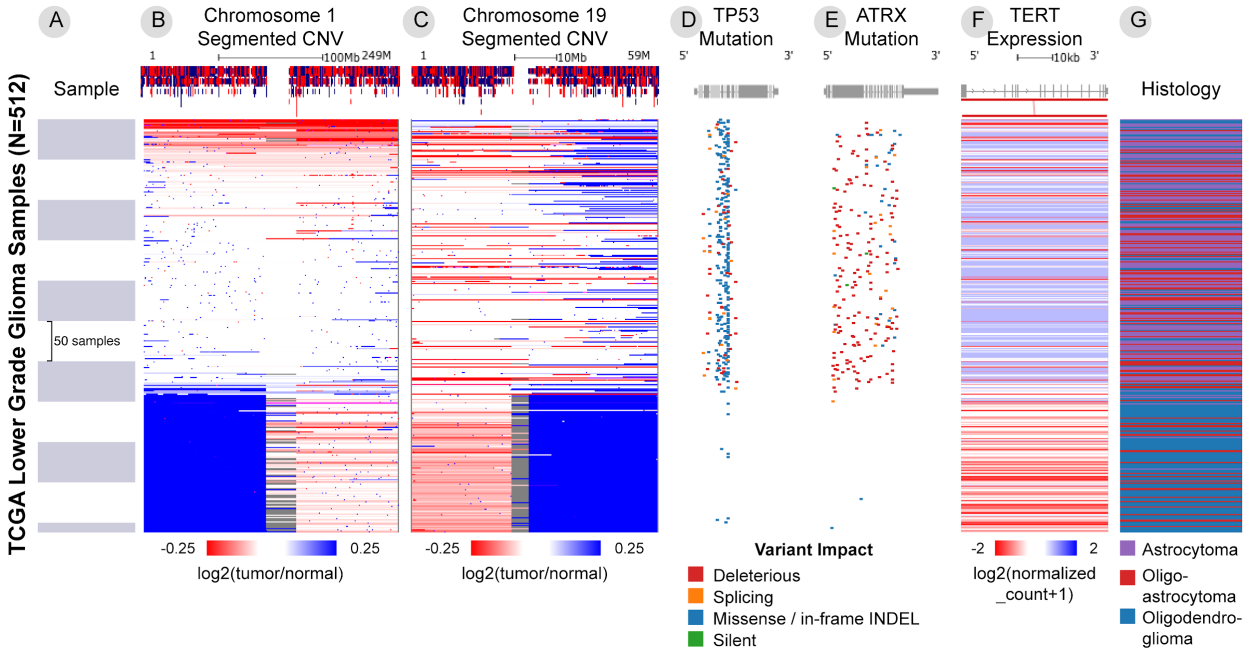


Figure 2. Xena Visual Spreadsheet showing the separation of TCGA lower grade gliomas into two groups. Samples in the bottom group are characterized by loss of chromosome arms 1p and 19q and relatively high expression of TERT. Samples in the top group are enriched for TP53 and ATRX mutations. Each row in the spreadsheet corresponds to a single sample (n=512). The first column shows the scale of samples. The rows are sorted by the left most data column (B) and sub-sorted on subsequent columns. Starting from the left, data columns are chromosome 1 and 19 copy number variations, TP53 and ATRX mutation status, TERT gene expression, and sample histology. Copy number columns (B, C) show genes at the top: red for the forward strand, dark blue for the reverse strand. Colors within the column indicate amplifications in red and deletions in blue. Mutation columns (D, E) show a gene diagram at the top with exons in grey boxes, with tall coding regions and short untranslated regions. The position of each mutation is marked in relation to the gene diagram and colored by its functional impact: deleterious mutations are red, missense and in-frame indels are blue, splice mutations are orange, and synonymous mutations are green. Gene expression (F) is colored red to blue for high to low expression. Samples at the top are enriched for the astrocytoma histological subtype, while the samples at the bottom tend to be the oligodendroglioma subtype (G).
https://xenabrowser.net/heatmap/?bookmark=3ddc01c001c0020ce1d3060a66f5cb64

Figure 3

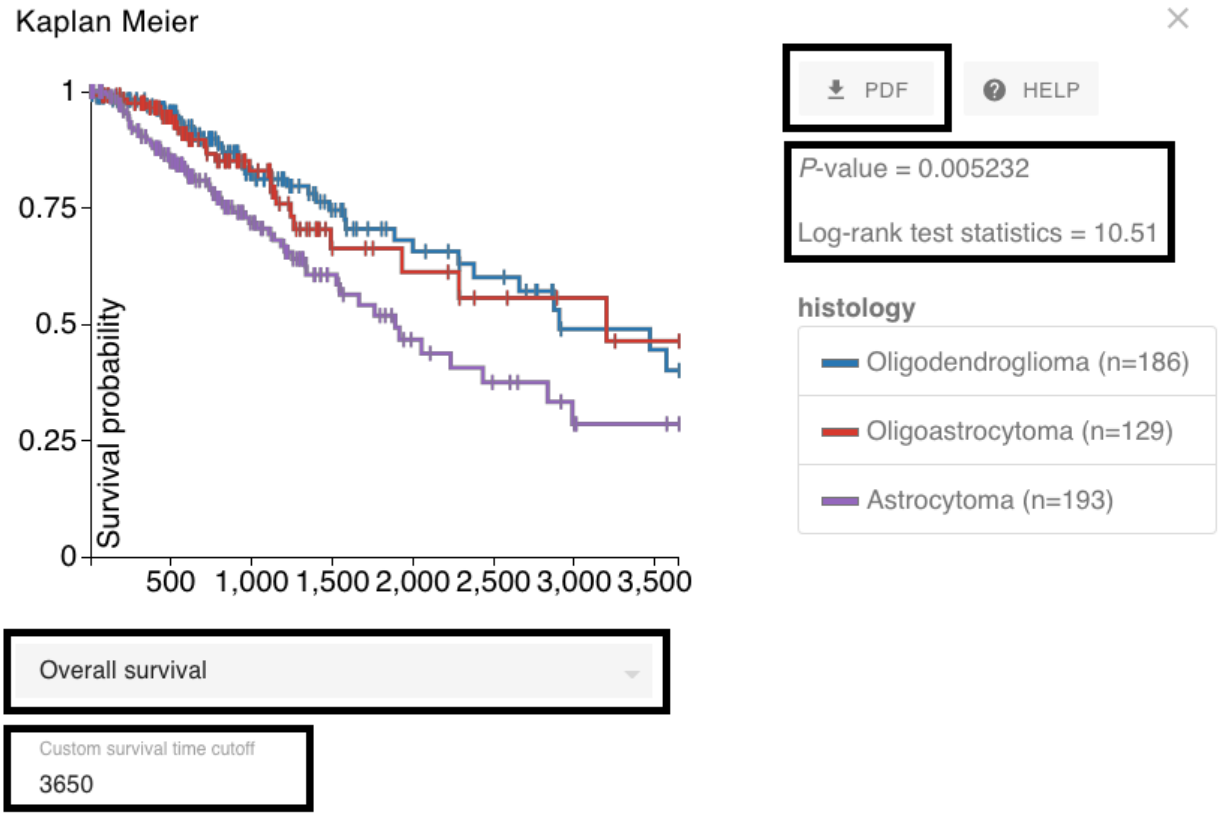


Figure 3. Kaplan-Meier analysis of overall survival for TCGA lower grade glioma histological subtypes. Black boxes in the figure highlight, top to bottom, a button to generate a PDF, the statistical analysis results, a dropdown menu to select different survival endpoints such as overall or recurrence-free survival, and a textbox to enter a custom survival time cutoff (currently set to 3,650 days, or 10 years). This figure shows that patients characterized as having the astrocytoma histological subtype have significantly worse 10-year overall survival compared to the oligodendroglioma and oligoastrocytoma subtypes ($p < 0.05$).
https://xenabrowser.net/heatmap/?bookmark=2f9d783982879594dd0f52564058372d

Figure 4

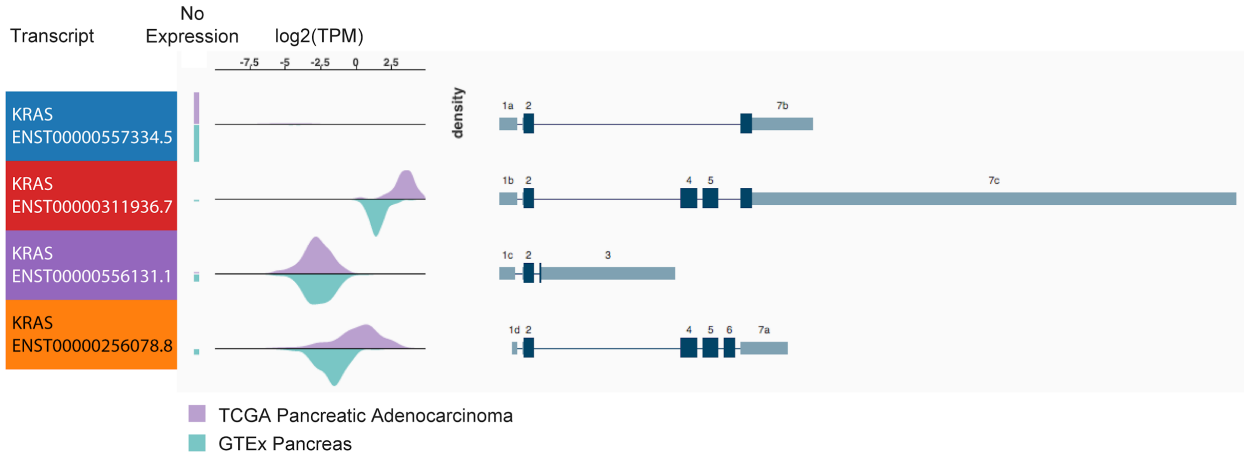
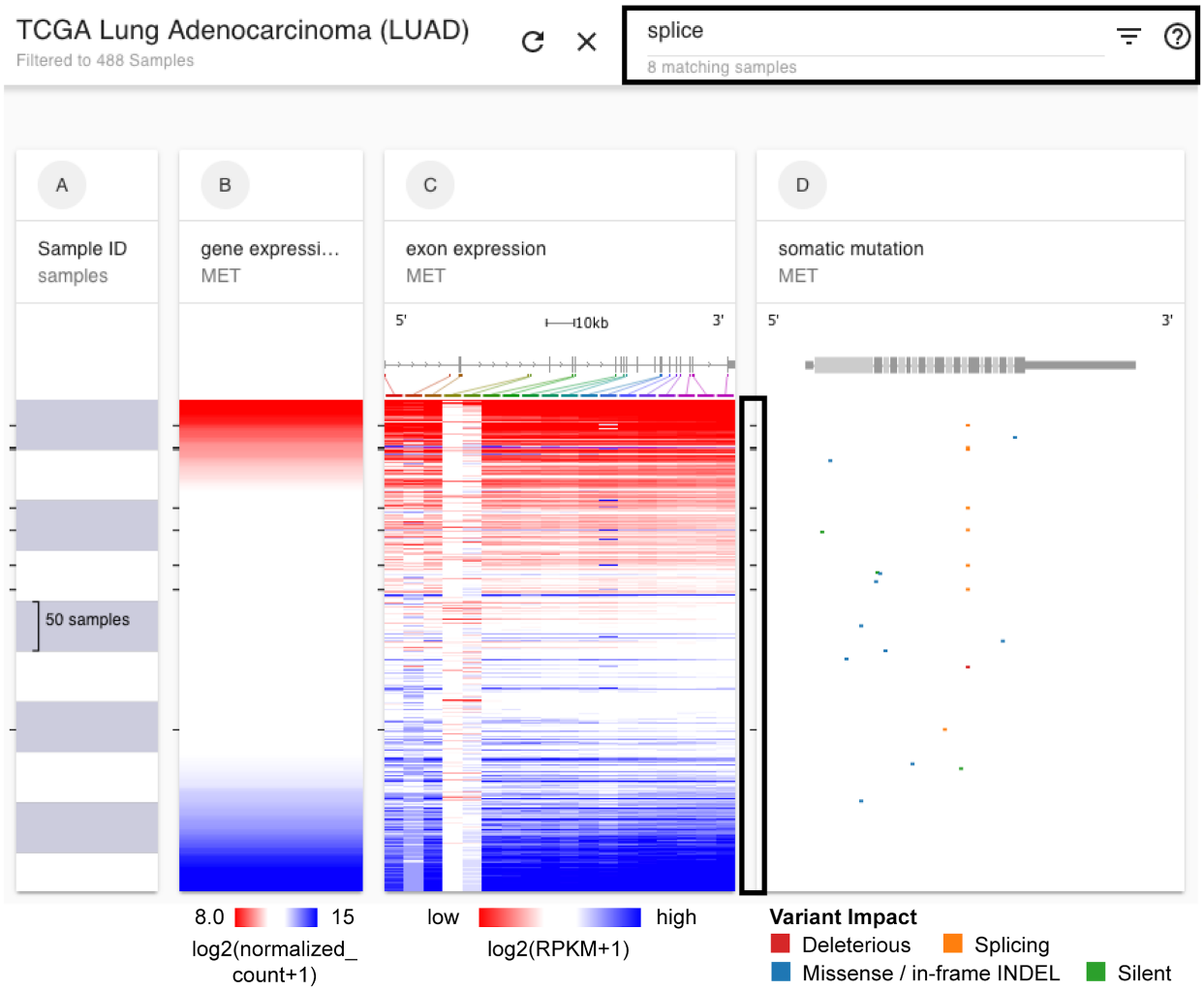


Figure 4. Transcript View in Xena showing four KRAS transcripts' expression for TCGA pancreatic adenocarcinoma and GTEx normal pancreas tissue. To generate a view, a researcher enters a gene and select two populations. The visualization will display, for all transcripts for that gene, a double (top and bottom) density distribution of transcript expression in each population. We see that for KRAS, transcript ENST00000311936.7 (second from the top), has higher expression in pancreatic tumors (TCGA) compared to the normal pancreas tissue (GTEx).
https://xenabrowser.net/transcripts/?bookmark=b832d9683cd8914aad0215b616bd5b21

Figure 5

a.


TCGA Lung Adenocarcinoma (LUAD)
Filtered to 488 Samples
splice
8 matching samples
A
Sample ID
samples
50 samples
B
gene expressi...
MET
C
exon expression
MET
5'
10kb
3'
D
somatic mutation
MET
5'
3'
8.0
15
log2(normalized_
count+1)
low
high
log2(RPKM+1)
Variant Impact
Deleterious
Splicing
Missense / in-frame INDEL
Silent

b.

Figure 5. Xena Browser text-based find, highlight, filter, and subgroup samples functionality. **(a)** Finding and highlighting samples in TCGA lung adenocarcinoma cohort that have a splice mutation in the gene *MET*. Similar to the 'find in document' feature in Microsoft Word, users can search all data on the screen. In this figure, the Xena Browser searched all columns for the user's search term 'splice' and highlighted samples with a 'splice' mutation with black tick marks (indicated by the black box). More complex search terms can include 'AND', 'OR', '>', '<', '=', and more. Users can dynamically filter, zoom, and create subgroups based on the search results. Columns from left to right are MET gene expression, MET exon expression and MET somatic mutation status.
https://xenabrowser.net/heatmap/?bookmark=72f202204506cbadb2f3ab3880d4bf75
(b) After creating a new column with two subgroups. Columns are same as (a) with the user-generated column inserted on the left. Samples that matched the query of 'splice' were assigned a value of "true" and those that do not "false". The researcher has zoomed to a few samples at the top for a more detailed view. The figure shows that samples that have the splice site mutation (orange, column E) have lower expression of exon 14 within the MET gene (column D). The splice mutation causes exon 14 skipping and results in the activation of MET (Kong-Beltran 2006, The Cancer Genome Atlas Research Network 2014).
https://xenabrowser.net/heatmap/?bookmark=6310fab5a8e44933b16ff7766b6f01ee

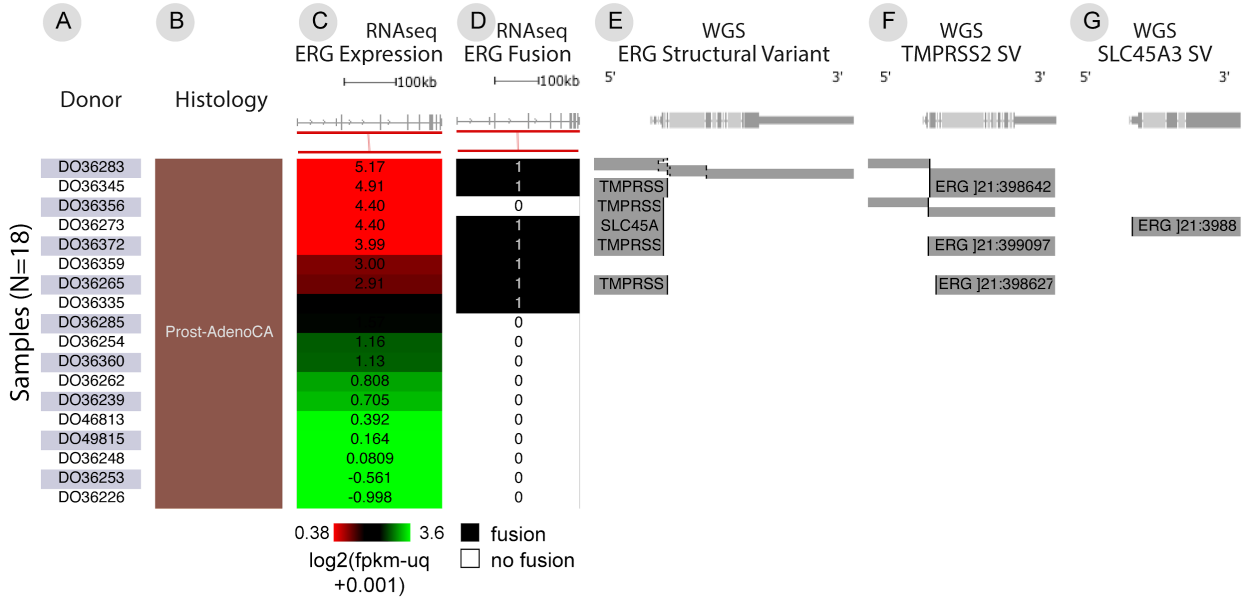
Table 1

Public Xena Resources	Samples	Data Types
TCGA	12,470	copy number, gene-, exon-, miRNA-, and protein-expression, somatic mutation, DNA methylation, survival, and clinical data
Pan-cancer Atlas	12,591	copy number, gene-, miRNA-, and protein-expression, somatic mutation, DNA methylation, molecular subtypes, curated survival, and clinical data
ICGC	17,697	copy number, gene expression, somatic coding mutation, and somatic whole-genome mutation (non-TCGA only)
PCAWG	2,834	whole-genome copy number, somatic mutations, large structural variants, gene- and miRNA-expression, RNAseq based gene fusion, alternative promoter usage, RNAseq based slicing events, purity, ploidy, mutational signature, survival, and curated histology
UCSC Toil RNAseq Recompute	19,131	TCGA, TARGET and GTEx gene and transcript expression
GDC	20,157	copy number, somatic mutations, gene and miRNA expression, overall survival, and phenotypes
Treehouse	11,258	TCGA, TARGET and Treehouse partnering clinical samples gene and transcript expression
UCSC Public	27,072	Somatic mutation, gene expression, copy number, and clinical data from 45 studies using adult and pediatric tumors, cell lines, mouse models or single cells.

Table 1. Summary of data hosted on Public Xena Hubs.

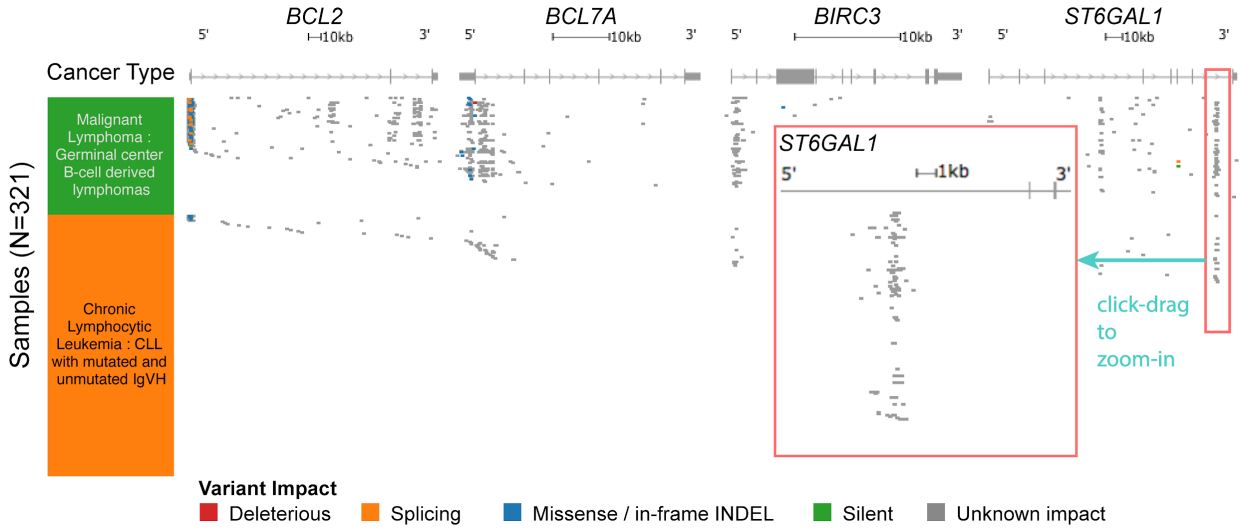
Supplemental Figures

Supplemental Figure 1



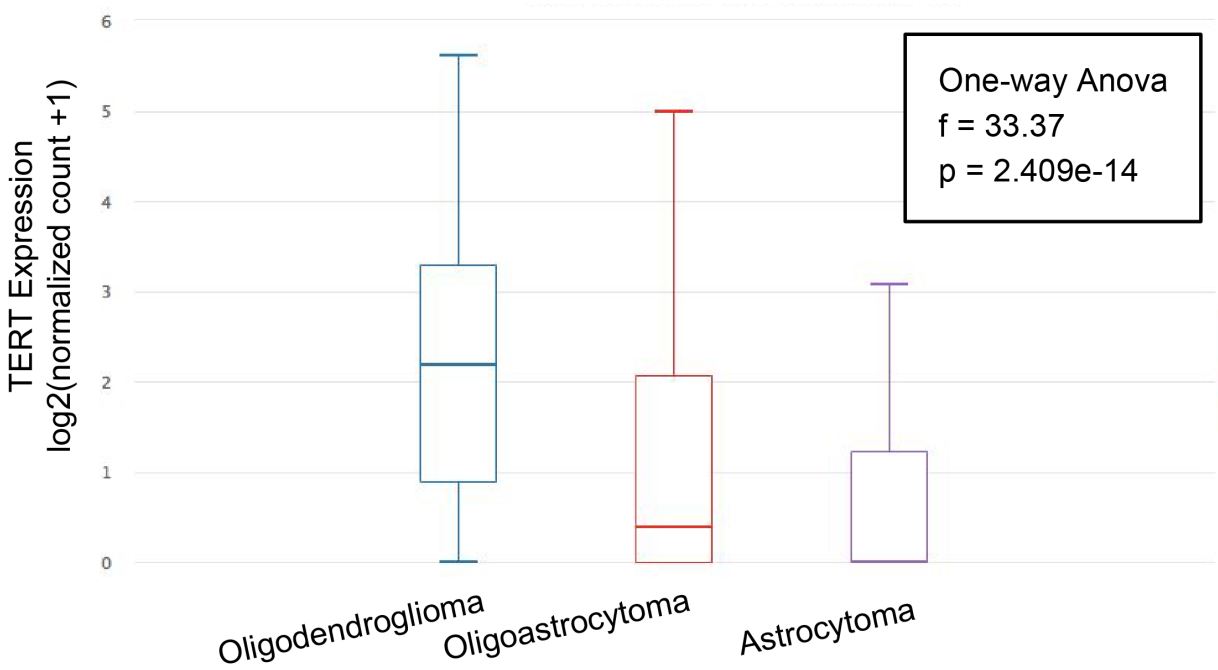
Supplemental Figure 1. Visualization of large structural variants. This figure shows frequent ERG fusion in PCAWG prostate cancer detected by both RNA-seq and DNA-seq analysis. The left three data columns (B, C, D) are histology, ERG gene expression, and ERG fusion detected using RNA-seq data. Gene expression is colored red to green for high to low expression. In the ERG fusion column (D), samples that have a fusion are marked with 1 and those that do not are marked with 0. The next three columns (E, F, G) show structural variant calls made using whole-genome DNA-seq data for ERG, TMPRSS2, and SLC45A3. Precise breakpoints are mapped to gene diagrams. A grey bar indicates an external piece of DNA that is fused at the breakpoint. Gene names on the grey bars show the origin of the external DNA that is joined. This figure shows that TMPRSS2 and SLC45A3 are fusion partners for ERG, and that these fusions correlate with over-expression of ERG. Fusions detected by RNA-seq and whole-genome sequencing are not always consistent. Here, even using a consensus of DNA-based detection methods, one fusion detected by a consensus of RNA-based detectors is missed, and the converse is also seen. This example shows that an integrated visualization across multiple data types and algorithms provides a more accurate model of a genomic event.
https://xenabrowser.net/heatmap/?bookmark=92db485580786d1ef14c6c06b680201b

Supplemental Figure 2



Supplemental Figure 2. Visualization of both coding and non-coding mutations from a gene-centric perspective in ICGC lymphomas. The columns left to right are cancer type, BCL2, BCL7A, BIRC3 and ST6GAL1 mutation status, respectively. Gene diagrams are shown at the top of each column, with exons as gray boxes, introns as lines. The position of each mutation is marked in relation to the gene diagram and colored by its functional impact, with deleterious mutations in red, missense mutations and in-frame indels in blue, splice site mutations in orange, synonymous mutations in green,, and mutations with an unknown functional impact in grey. This figure shows the intronic mutations hotspots in these genes. These mutation 'pile-ups' would be not be visible if viewing exomes only. A dynamic toggle allows user to show or hide introns from the view. While the majority of the intronic mutations in this view have an unknown impact (shown in grey), they overlap with known enhancers regions (Mathelier 2015). Insert is a zoomed-in view of one of the hotspots in ST6GAL1. Users click-and-drag on the gene diagram to trigger zoom.
https://xenabrowser.net/heatmap/?bookmark=a11909d2c2c629ee999e1a9802fac7dd

Supplemental Figure 3



Supplemental Figure 3. Xena Chart View showing a box plot of TERT expression for each of the TCGA lower grade glioma histological subtypes. Columns created in the Visual Spreadsheet (Figure 2) are used to construct the chart. Statistical analyses are automatically computed. This view shows a significant expression difference for TERT between oligodendroglioma, oligoastrocytoma and astrocytoma histologies (one-way ANOVA, $p < 0.05$).
https://xenabrowser.net/heatmap/?bookmark=77a8506961f7c16275416bcaf2c1f08b

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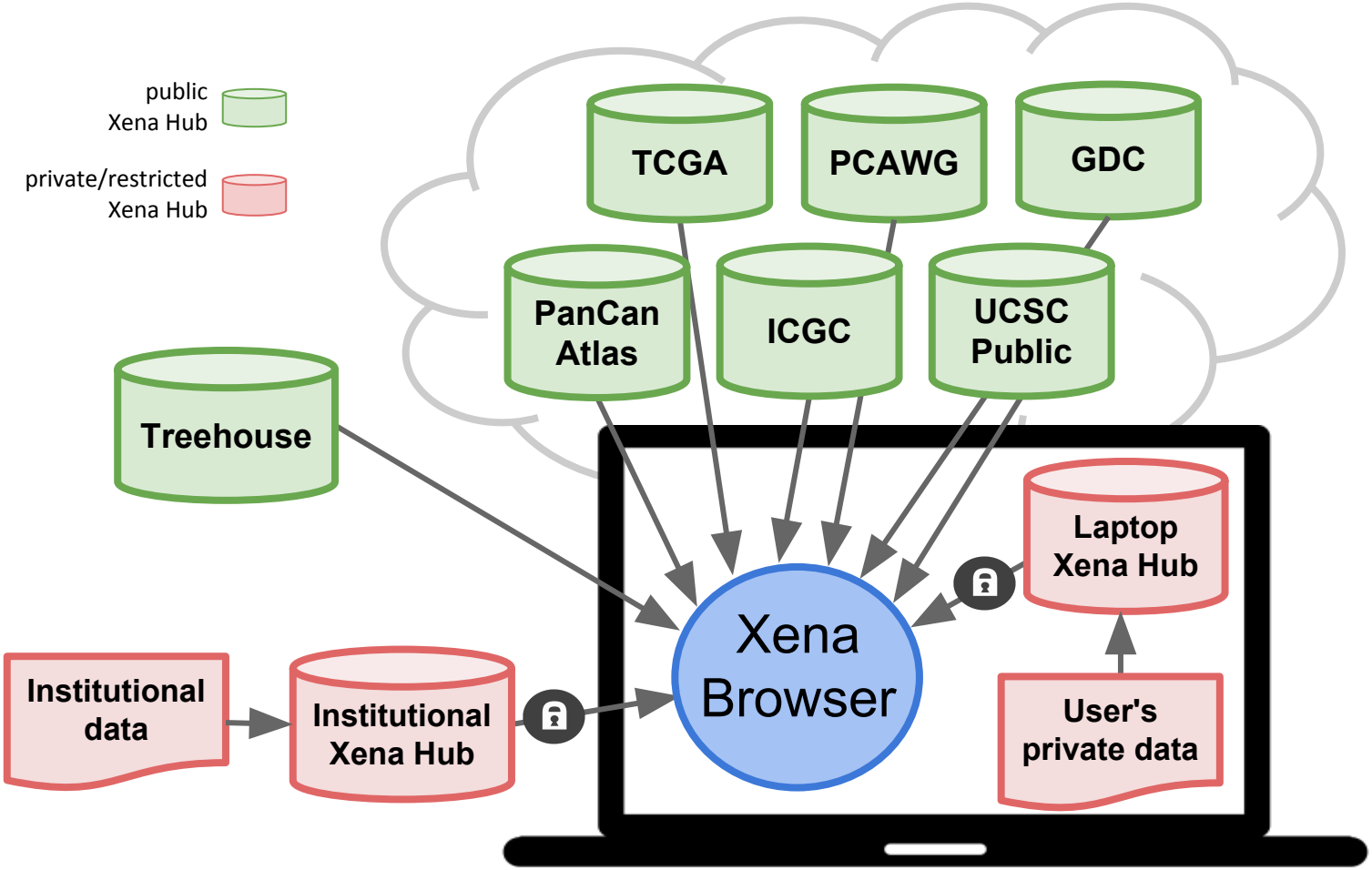
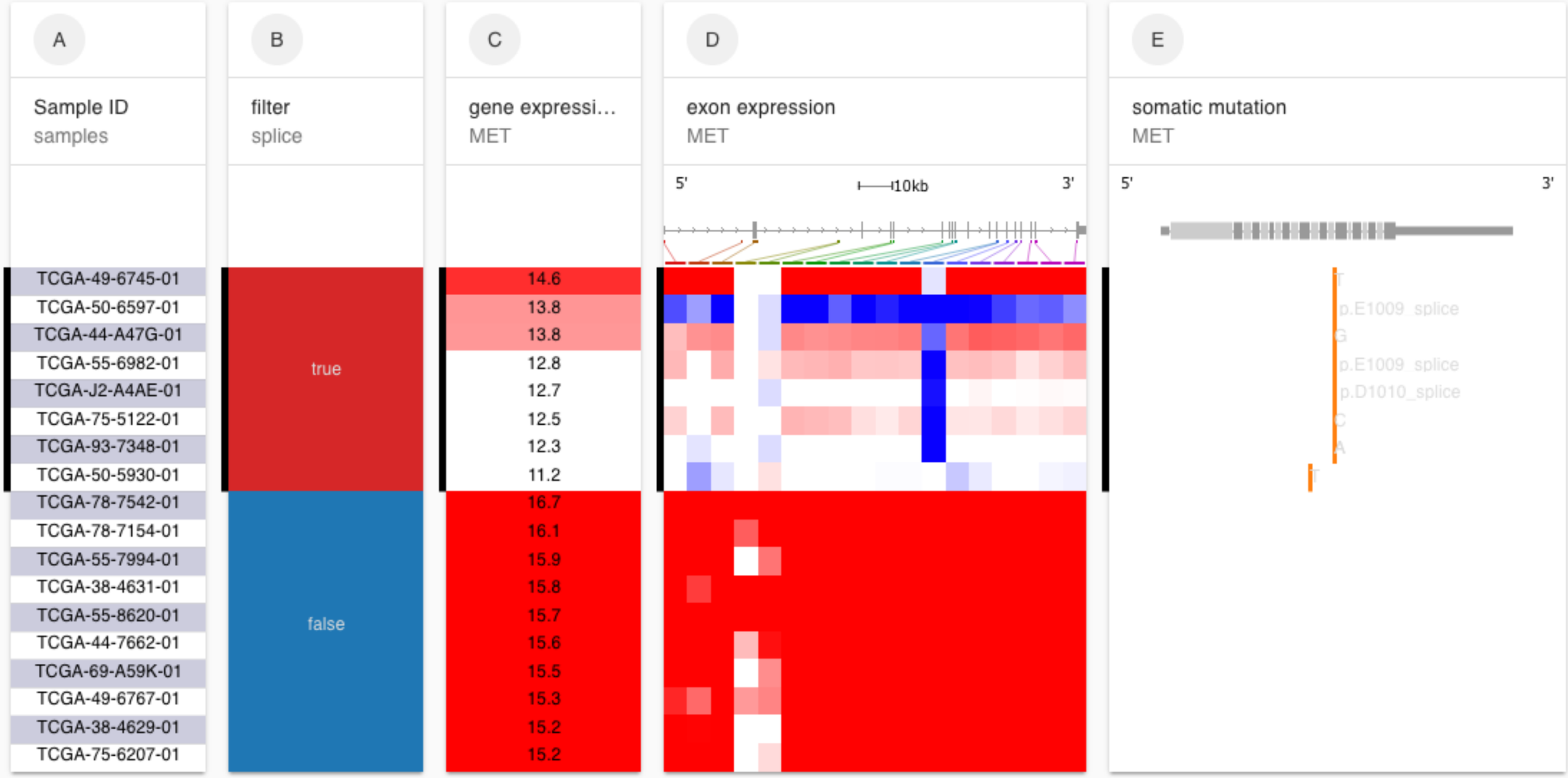

public
Xena Hub
private/restricted
Xena Hub
TCGA
PCAWG
GDC
PanCan
Atlas
ICGC
UCSC
Public
Treehouse
Laptop
Xena Hub
Xena
Browser
Institutional
data
Institutional
Xena Hub
User's
private data

TCGA Lung Adenocarcinoma (LUAD)

Filtered to 488 Samples - Zoomed to 1 - 18

Splice

8 matching samples



8.0 15

log2(normalized_count+1)

low high

log2(RPKM+1)

Variant Impact

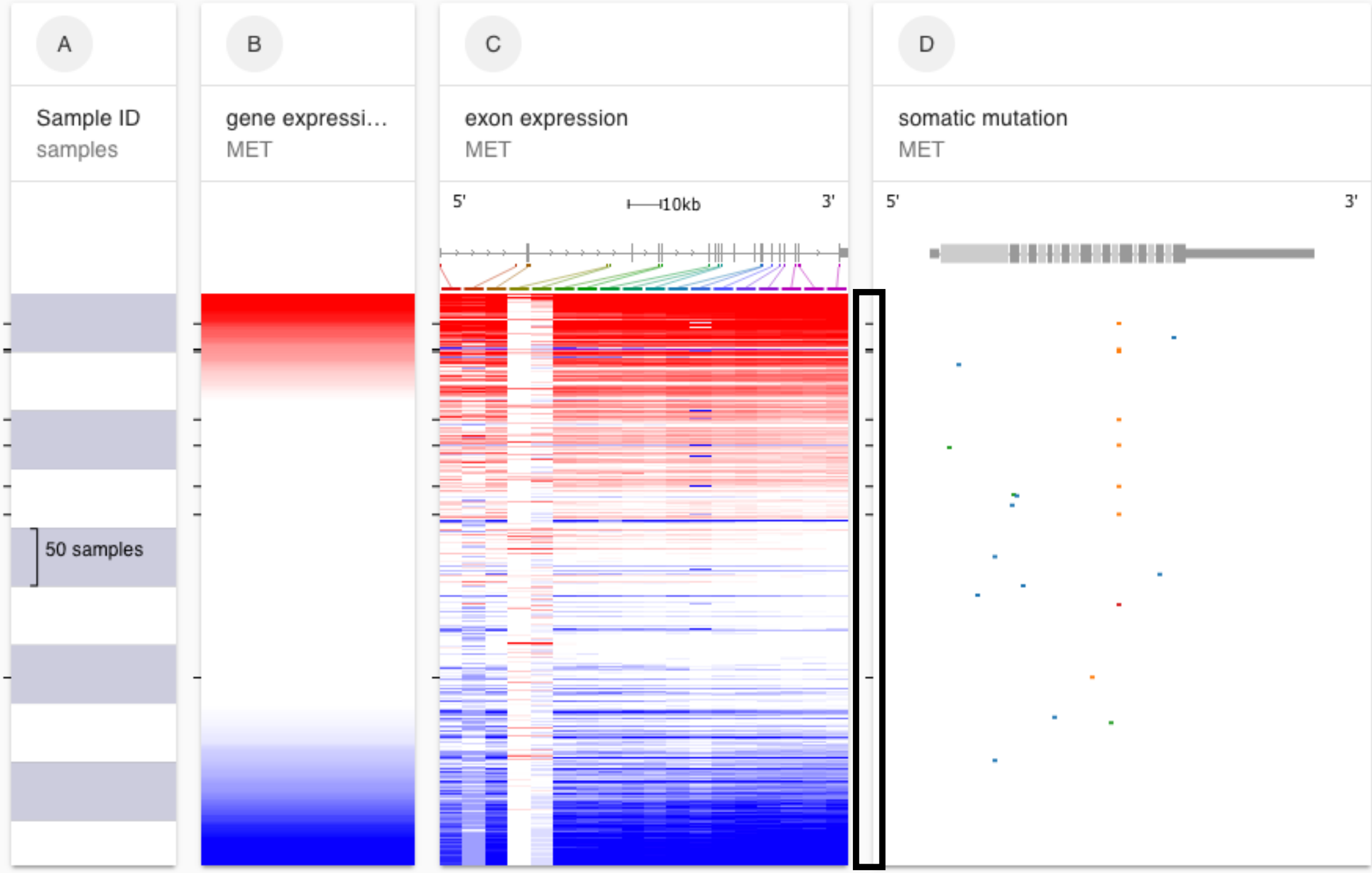
Splicing

TCGA Lung Adenocarcinoma (LUAD)

Filtered to 488 Samples

splice

8 matching samples



8.0 15

log2(normalized_ count+1)

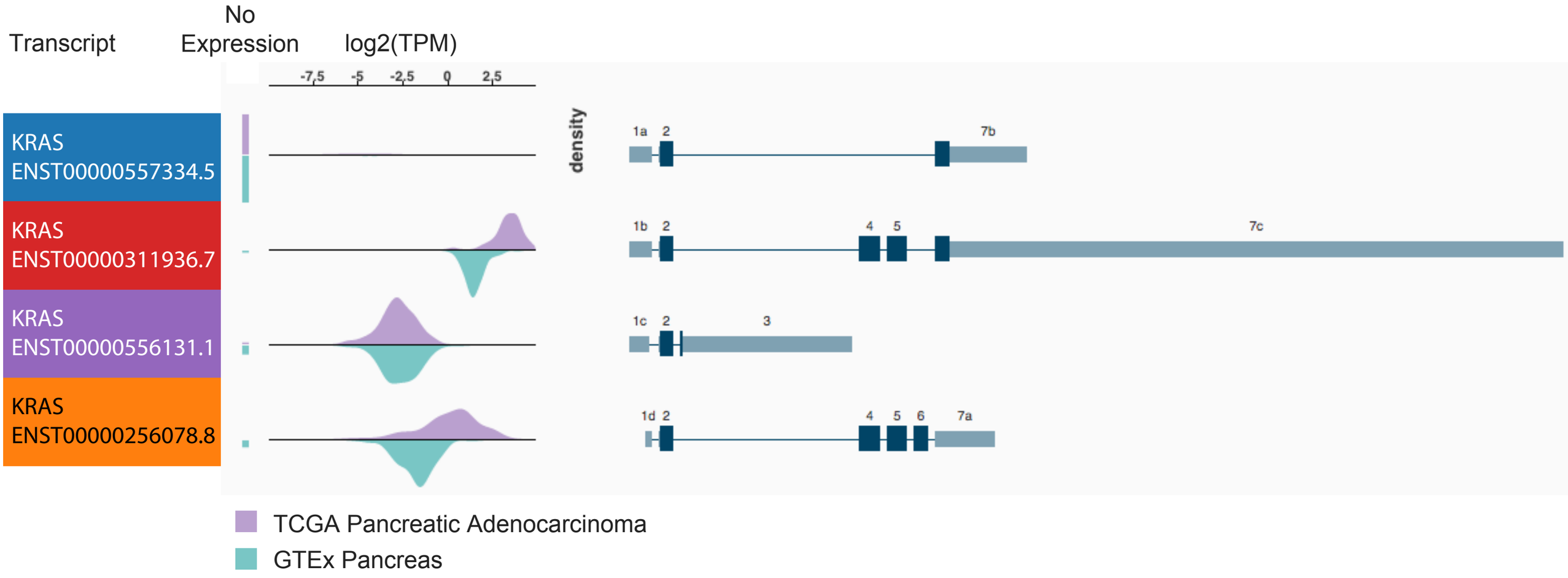
low high

log2(RPKM+1)

Variant Impact

Deleterious Splicing

Missense / in-frame INDEL Silent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2.5
density
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KRAS ENST00000556131.1
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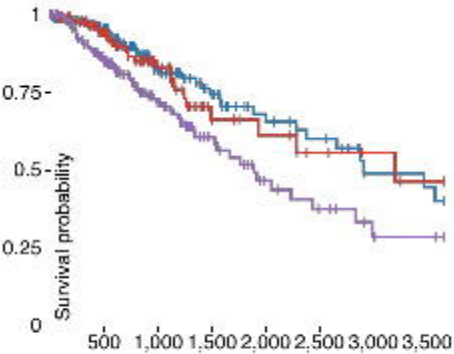
1a 2 7b
1b 2 4 5 7c
1c 2 3
1d 2 4 5 6 7a
TCGA Pancreatic Adenocarcinoma
GTEx Pancreas

Kaplan Meier



PDF

HELP

P-value = 0.005232

Log-rank test statistics = 10.51

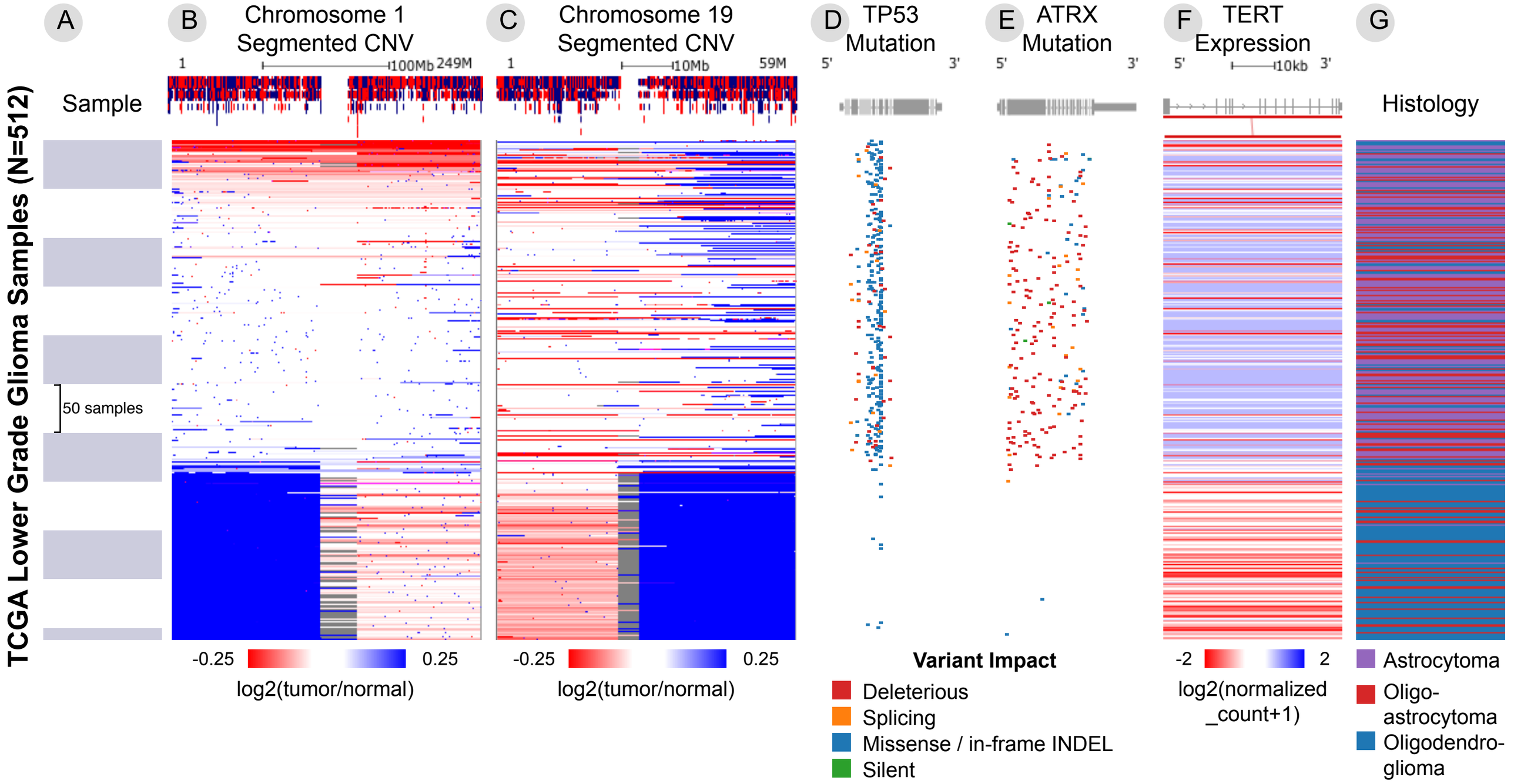
histology

- Oligodendroglioma (n=186)
- Oligoastrocytoma (n=129)
- Astrocytoma (n=193)

Overall survival

Custom survival time cutoff

3850


A
B
Chromosome 1
Segmented CNV
C
Chromosome 19
Segmented CNV
D
TP53
Mutation
E
ATRX
Mutation
F
TERT
Expression
G
Histology
Sample
TCGA Lower Grade Glioma Samples (N=512)
50 samples
1
100Mb
249M
1
10Mb
59M
5'
3'
5'
3'
5'
10kb
3'
-0.25
0.25
log2(tumor/normal)
-0.25
0.25
log2(tumor/normal)
Variant Impact
Deleterious
Splicing
Missense / in-frame INDEL
Silent
-2
2
log2(normalized
_count+1)
Astrocytoma
Oligo-
astrocytoma
Oligodendro-
glioma