

Tutorial

Background

Cancer genomics studies have transformed the field of Oncology, from more accurate diagnostic tests to precision treatment. However, cancer genomics studies produce massive, heterogeneous datasets with variable technical characteristics, study parameters, and ontologies. Some of these characteristics include the preprocessing of data, file formats, attribute names, and or reference material. These inconsistencies between different studies and datasets create challenges for data integration, analysis, interpretation of results, and extrapolation of meaningful observations. Consequently, attempting to utilize, analyze, or combine datasets from multiple sources proves inefficient and overly complicated. OncoMX (https://www.oncomx.org/) is a knowledgebase and web portal actively being developed to quell such challenges by leveraging biomedical ontologies to unify disparate data while emphasizing the availability of multi-faceted evidence for cancer biomarkers. With advances in cancer genomics technologies, studies regarding cancer biomarkers have become an integral aspect of cancer research. A biomarker can be defined as a measurable (proteomic, genomic, metabolomic, epigenetic, etc.) substance in an organism that indicates the occurrence of disease, infection, or possibly environmental exposure. Genomic biomarkers, such as mutations in the BRCA1 and BRCA2 genes, are examples of highly penetrant biomarkers whose upregulation significantly increases the incidence of breast cancer. In response to the influx in cancer genomic data, OncoMX has created a space to explore multiple data sources in one database.

What is OncoMx?

OncoMX is a knowledgebase and web portal developed to address many of the aforementioned challenges by streamlining searches between unified datasets. OncoMX is a collaborative project between The George Washington University, NASA's Jet Propulsion Laboratory, the Swiss Institute of Bioinformatics, and the University of Delaware. The collective OncoMX mission is to create an integrated cancer mutation and expression resource for exploring cancer biomarkers to improve early cancer detection. OncoMX currently integrates sequencing-based mutation data from BioMuta, cancer/normal differential expression data from BioXpress, normal expression data across organisms from Bgee, biomarker data from EDRN, and literature mining through custom applications of DEXTER and DiMeX.

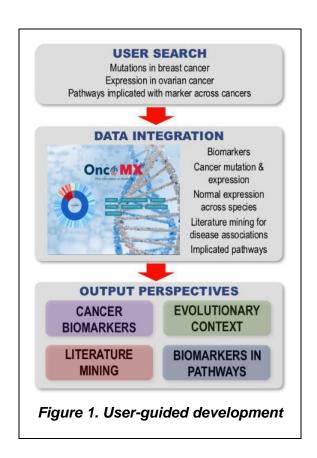
BioMuta and BioXpress serve as the foundational knowledgebases for OncoMX, where data is unified through Disease Ontology and Uberon Anitomical Entity terms. BioMuta is a database of single nucleotide variations (SNVs) associated with cancer, where variations are mapped to genomic coordinates and RefSeq nucleotide entries, and unified through UniProtKB/Swiss-Prot positional coordinates. BioXpress is a database of RNA-Seq and miRNA-seq expression data that has been analyzed for differential expression associated with cancer.

Normal expression data from Bgee is added to give context to the differential expression analysis. Bgee is a database of annotated gene expression evolution data from model organisms. Gene expression data in Bgee is annotated with Uberon Anatomical Entity terms, Developmental State terms, homology ontology, and confidence information ontology. EDRN is a database of cancer biomarker information which facilitates the synthesis of clinical applications from biomarker information, early cancer state testing, and cancer risk testing. Finally, the custom literature mining software DEXTER and DiMeX augment the cancer data to improve functional interpretation of the reported variants and expression profiles. DEXTER is an automated literature-mining tool

that extracts gene and miRNA expression information associated with disease from literature, whereas DiMeX extracts relationships about mutation in cancer.

Supplemental data currently being integrated into the OncoMX database include functional annotations, scRNA-seq analysis, neoepitopes caused by mutations in cancer, and updated cancer mutation and expression literature mining results. OncoMX also houses custom datasets through the parallel data site at data.oncomx.org.

OncoMX was designed, with key user input, to better facilitate cancer biomarker research and discovery through four major use cases: 1) exploration of cancer biomarkers, 2) evaluation of mutation and expression in an evolutionary context, 3) side-by-side exploration of published literature for mutation and expression in cancer, 4) and exploration of a specific gene or biomarker within a pathway context (see Figure 1). OncoMX is expected to benefit basic cancer research, promote efficient consumption of information by end users, and ultimately improve biomarker and cancer detection capabilities. The unification of multiple cancer datasets allows users to explore or generate hypotheses within one database, execute targeted searches, and compare data sources. OncoMX is projected to support a broad range of cancer research initiatives for the enrichment of cancer biomarker detection. This work is licensed under a Creative Commons Attribution 4.0 International License.



Where to start

The OncoMX dashboard has everything accessible within a few clicks (see Figure 2). The main OncoMX donut graph in the center of the page is an interactive graph comprising all the data integrated into OncoMX. By moving the cursor over the different sections of the circle, the user is able to see the data contributed by each resource. For example, when holding the cursor over the large dark blue sections of the donut, 33,172,849 data points are shown to be contributed from Bgee. By then clicking on the dark blue Bgee portion, the view expands to show another donut graph, broken down into subcomponents of Bgee data. On the outer edges, there are four segments containing links to additional useful information. The "Perspectives" list (in progress) will provide links to dashboards optimized for the four main use case perspectives. "Data Source" provides links to access all the original data integrated into OncoMX. "Statistics at a Glance" offers a statistical summary organized by data

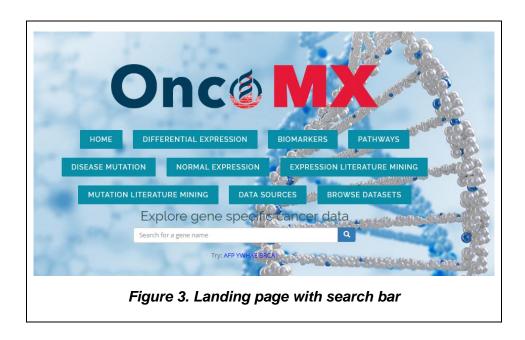
source, and "News" displays a news feed of pertinent announcements and will eventually link to social media feeds. Clicking on any of the options in the tables leads you to specific data tables lower on the homepage or links out to separate pages with the corresponding information.



How to search

For the purposes of this tutorial, we will use the following biological question to demonstrate OncoMX features: <u>Is the BRCA1 gene only upregulated in breast cancer?</u>

As described above, options for exploring various contributing datasets can be accessed from the landing page (see Figure 3). The search bar can be found below the buttons for exploring datasets.



The user can perform a global search by entering either a gene symbol or a UniProtKB accession in the search box. This will allow the user to access different visualizations associated with the searched gene of interest. Further down in this tutorial, a use case is provided detailing how to perform a search and view and interact with the results. The user can navigate back to the OncoMX main page from the search results (or from any page) by clicking the "Home" tab in the upper menu bar or by clicking on the OncoMX logo.

Explore datasets

As described above, the landing page has a number of options available for quick exploration of integrated datasets. Currently available data types include: Differential Expression, Biomarkers, Pathways, Disease Mutation, Normal Expression, Expression Literature Mining, and Mutation Literature Mining. The information included in each of these datasets is explained below.

Differential Expression

This table is indexed by gene/protein/mRNA or miRNA accession/name. In addition to text searching, you can use the filters on the left hand side of the table to filter rows by TCGA cancer types or by significance of differential expression. To access the gene detail view for a specific entry, click the hyperlinked gene symbol in the first column. Cross-references to numerous other resources can also be found in the table, including NCBI gene search, BioXpress entry, disease ontology, TCGA study, and Uberon ontology.

Column headers and descriptions for this table are as follows:

- Gene/miRNA: Official gene symbol approved by the HGNC, which is a short abbreviated form of the gene name, hyperlinked to the OncoMX detail view for this entry; if miRNA, this column will report the accession in the miRBase database
- UniProtKB/SwissProt AC: Hyperlinked UniProtKB accession (accession assigned to the protein isoform chosen to be the canonical sequence in UniProtKB database) linking to relevant entry in BioXpress
- **P-value:** P-value associated with reported differential expression
- Adj. P-value: P-value associated with reported differential expression adjusted for multiple testing
- Cancer Type: Mapped Cancer Disease Ontology slim term and link to relevant disease ontology page
- Log2 F.C.: Log2 fold change of expression of the gene/miRNA in tumor as compared to adjacent normal
- Patient Freq.: Proportion of patients whose individual observed trend of expression matches the cancer-wise trend
- RefSeq AC: RefSeq accession associated with the transcript
- **Significant**: Reports whether the observed change in expression was determined to be significant (adjpval < 0.05)
- TCGA Cancer: TCGA cancer acronym linked to the corresponding TCGA study page in NIH-NCI GDC Data Portal
- Anatomical Entity ID: Uberon anatomical entity ID corresponding to the diseased tissue

Biomarkers

This table is indexed by gene symbol or panel name.

Column headers and descriptions for this table are as follows:

- **Gene Symbol/Panel:** Official gene symbol or panel name, hyperlinked to the OncoMX detail view for this entry
- Type: Type of biomarker (can be Epigenetic, Gene, Genomic, Protein, or Proteomic)

- Associated Dataset: Dataset(s) associated with the biomarker as reported in EDRN database
- **Is Panel**:Denotes if entry is a biomarker or a panel
- Phase: Please see EDRN documentation
- QA State: Denotes whether biomarker has been curated, accepted, or is under review
- Organ: Organ in which biomarker is applicable (current options include Colon, Lung, Breast, and Ovary)
- **HGNC Symbol**: Official gene symbol approved by the HGNC, which is a short abbreviated form of the gene name
- Reference Resource: Hyperlinked references reporting biomarker activity
- **UniProtKB/SwissProt AC**:Accession assigned to the protein isoform chosen to be the canonical sequence in UniProtKB database (not applicable to panels)

Pathways

This table is indexed by UniProtKB/SwissProt AC and reports events associated with a given protein, its evidence, and the pathway to which the event belongs.

Column headers and descriptions for this table are as follows:

- **UniProtKB/SwissProt AC**: Accession assigned to the protein isoform chosen to be the canonical sequence in UniProtKB database hyperlinked to UniProtKB
- **Gene Symbol:** Official gene symbol approved by the HGNC, which is a short abbreviated form of the gene name, hyperlinked to the OncoMX detail view for this entry
- Event: Name of pathway event
- Evidence Code: Evidence code for gene/protein participation in the event (can be IEA or TAS)
- Reactome Pathway ID: Hyperlinked Reactome IDs for the corresponding pathway

Disease mutations

This table reports variants in cancer samples for each relevant in genomic and proteomic coordinates.

Column headers and descriptions for this table are as follows:

- **Gene Symbol**: Official gene symbol approved by the HGNC, which is a short abbreviated form of the gene name, hyperlinked to the OncoMX detail view for this entry
- UniProtKB/SwissProt AC: Hyperlinked UniProtKB accession (accession assigned to the protein isoform chosen to be the canonical sequence in UniProtKB database) linking to relevant entry in BioMuta
- RefSeq AC: RefSeq accession associated with the canonical transcript
- Cancer Type: Type of cancer associated with reported variant
- Functional Impact: Denotes whether a reported variant is associated with a functional loss or gain of acetylation, phosphorylation, glycosylation, or other functional annotation from UniProtKB, or prediction from PolyPhen or NetNGlyc2.0
- **Genome Position**: Genomic position of the variant
- **Nuc. Position:** Position of variant in nucleic acid sequence
- **Ref. Nuc:** Reference or wild-type nucleotide base
- Var. Nuc: Nucleotide base resulting from variation
- AA Position: Position of variation in protein sequence
- Ref. AA: Reference or wild-type amino acid residue
- Var. AA: Amino acid residue resulting from variation

- **Polyphen2:** If applicable, lists the predicted effect of the variant reported by PolyPhen-2 (benign, possibly damaging, or probably damaging)
- **PMID:** If available, PMID(s) of manually curated or semi-automatically mined (using DiMeX) publication(s) associated with the reported variation
- Source: Data source of reported variation (can be CIViC, ClinVar, COSMIC, ICGC, or TCGA)
- Status: Status of study from which variation was obtained (LG for large-scale, SM for small-scale)
- Anatomical Entity ID: Uberon anatomical entity ID corresponding to the diseased tissue

Normal expression

This table reports the status of RNA-seq derived expression in normal samples.

Column headers and descriptions for this table are as follows:

- **Gene Symbol**:Official gene symbol approved by the HGNC, which is a short abbreviated form of the gene name, hyperlinked to the OncoMX detail view for this entry
- **UniProtKB/SwissProt AC:** Accession assigned to the protein isoform chosen to be the canonical sequence in UniProtKB database
- Ensembl Gene ID: Hyperlinked Ensembl gene ID linking to relevant entry in Bgee
- Anatomical Entity Name: Uberon anatomical entity name corresponding to sample tissue
- Developmental Stage Name: Uberon developmental stage name corresponding to sample tissue
- Expression Call: Indicates presence or absence of expression
- Expression Rank: The lower the rank, the higher the expression level
- Call Quality: Quality associated with call (can be high quality or poor quality)

<u>EDRN</u>

This tab summarizes biomarker details from EDRN.

Colum header and descriptions are as follows:

- EDRN Title: Name given to biomarker in EDRN
- Organ: Organ in which biomarker is applicable (current options include Colon, Lung, Breast, and Ovary)
- **Phase:** If available, reports the designation of the biomarker as one of five phases (Phase 1, Preclinical Exploratory; Phase 2, Clinical Assay and Validation; Phase 3, Retrospective Longitudinal; Phase 4, Prospective Screening; Phase 5, Cancer Control)
- QA: Denotes whether biomarker has been curated, accepted, or is under review
- Aliases: Other names/descriptions of the biomarker
- **Description:** States the purpose and scope of the biomarker

Mutation literature mining

This table displays hits for literature-mined mentions of mutation in cancer using a customized application of DiMeX.

Column headers and descriptions for this table are as follows:

- **PMID**: PMID(s) of mined (using DiMeX) publication(s) containing variant information
- UniProtKB/SwissProt AC: Accession assigned to the protein isoform chosen to be the canonical

- sequence in UniProtKB database
- **Gene Symbol**: Official gene symbol approved by the HGNC, which is a short abbreviated form of the gene name
- Entrez ID: Unique, stable, and tracked integer identifier
- Gene Mention: Specific form/spelling of gene mentioned in the retrieved publication
- DOID: Mapped Cancer Disease Ontology slim ID
- **DOID Name**: Mapped Cancer Disease Ontology slim term
- Disease Mention: Specific form/spelling of disease mentioned in the retrieved publication
- Mutation Mention: Specific form of substitution mutation mentioned in the retrieved publication
- Mutation Type: Specifies whether the mutation is mentioned in terms of amino acid or nucleotide substitutions and coordinates
- Abstract Extraction: Section of abstract from which the relevant sentence was extracted
- Sentence Number: Number of sentence extracted
- Sentence Text: Text of sentence extracted
- Extraction Method: Denotes whether relationship in sentence was an association or other
- Patient/Control Numbers: If available, reports the number of patients and/or controls in the study
- Is Meta-Analysis: Denotes if the publication was a meta-analysis
- Is Review: Denotes if the publication was a review

Expression literature mining

This table displays hits for literature-mined mentions of expression in cancer for both genes and miRNAs using a customized application of DEXTER.

Column headers and descriptions for this table are as follows:

- UniProtKB/SwissProt AC: Accession assigned to the protein isoform chosen to be the canonical sequence in UniProtKB database
- Entrez ID: Unique, stable, and tracked integer identifier
- Gene Mention: Specific form/spelling of gene mentioned in the retrieved publication
- miRNA Number: Number/ID of miRNA mentioned in publication
- miRNA Mention: Specific form/spelling of miRNA mentioned in the retrieved publication
- **PMID:** PMID(s) of mined (using DEXTER) publication(s) containing expression information
- DOID: Mapped Cancer Disease Ontology slim ID
- **DOID Name:** Mapped Cancer Disease Ontology slim term
- **Disease Mention:** Specific form/spelling of disease mentioned in the retrieved publication
- Disease Extracted From: Section of the publication from which the disease mention was extracted
- Expression Level: Reports whether the expression change was reported to go up or down in disease
- Sentence Type: Type of sentence, strength of assertion is strongest is Type A
- Sample 1: Denotes the first (or only) group compared in the extracted sentence
- **Sample 2:** If the extracted sentence contains a comparison between two groups, denotes the second group compared in the extracted sentence
- **Is Same Patient:** Reports whether a comparison is performed between two groups of samples from a single patient
- Sentence Text: Text of sentence extracted

Explore statistics and data sources

In addition to providing access to datasets, the landing page also has options for accessing gene statistics and

downloading contributing datasets in their original forms.

Statistics at a Glance

As described above, clicking on any of the topics listed here or interacting with the Circos plot will toggle the charts displayed below. Statistics can be viewed as a series of charts across multiple resources (Total Cancer Terms and Proteins) or for each primary contributing resource (Biomarkers from EDRN, BioMuta, and BioXpress). Additional summary views will be added in subsequent releases.

Data Sources

The core underlying knowledgebase of OncoMX is derived from BioMuta and BioXpress integrated cancer mutation and expression databases. Normal expression data from Bgee and custom text mining software, DiMeX and DEXTER, augment the cancer data to improve functional interpretation of the reported variants and expression profiles. Where relevant, data are mapped to Disease Ontology and Uberon Anatomical Entity ontology terms to facilitate better integration. All data are wrapped into the OncoMX database and web portal, mapped to additional functional information from NCI Early Detection Research Network (EDRN) and Reactome. In version 1.0, cancer mutation and expression data are taken from: CIViC, ClinVar, COSMIC, ICGC, IntOGen, and TCGA.

While this section allows previewing of data sources, scrolling further down on the main page to the "External Downloads" section will provide access to full data dumps. Clicking any of the contributing source buttons will initiate a download.

For more information regarding pipelines of contributing resources, please refer to the following:

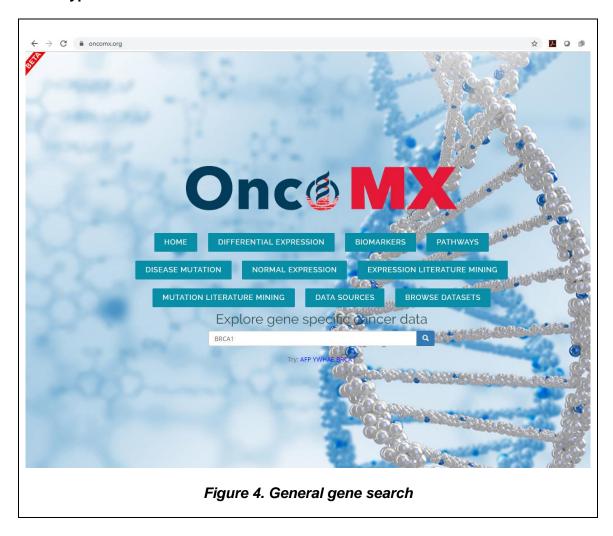
- Bgee: https://bgee.org/
- BioMuta: https://hive.biochemistry.gwu.edu/biomuta
- BioXpress: https://hive.biochemistry.gwu.edu/bioxpress
- DEXTER: https://academic.oup.com/database/article/doi/10.1093/database/bay045/5025486
- DiMeX: http://iournals.plos.org/plosone/article?id=10.1371/iournal.pone.0152725
- EDRN: https://edrn.nci.nih.gov/
- Reactome: https://reactome.org/

OncoMX use case

A major strength of the OncoMX portal is that the user can visualize all the data in one place for a specific gene by clicking on different tabs. The use case below illustrates how we can visualize all the different cancers expressed in a single gene including corresponding normal tissue expression and biomarkers in OncoMX. In this use case, we will use the example of BRCA1 to demonstrate search and overall website functionality.

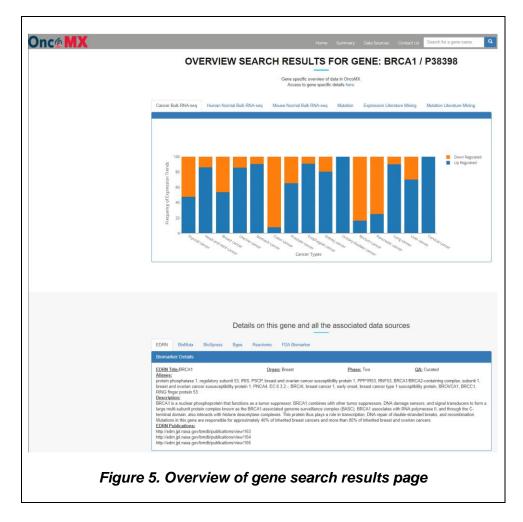
To search for the gene, go to the OncoMX homepage at www.oncomx.org and type your gene of interest in the search box. PLEASE NOTE: Throughout the use case, special formatting is used to distinguish between various types of text the user may see or input in the website. Labels within the portal are denoted by underlined, bold text, commands the user should perform are denoted in plain **bold text**, and data sources are denoted by italicized, underlined, bold text.

Step 1: In the search box type BRCA1

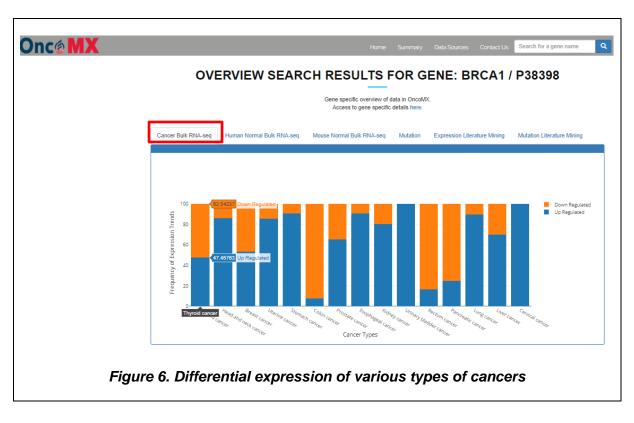


Step 2:

Click on **DIFFERENTIAL EXPRESSION** to explore the differential expression data. This will bring the user to a page that provides an overview of the search results for the gene of interest and other associated data of the gene of interest as illustrated below:



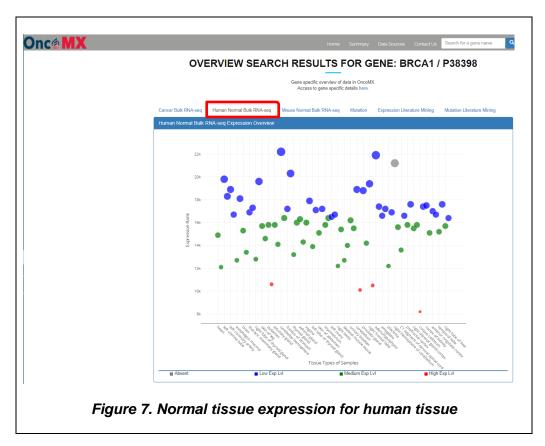
The first tab is a graphical representation of <u>Cancer bulk RNA-seq</u> which shows the frequency of expression trends for each cancer type. The blue bar denotes up-regulation where the orange shows down-regulation of the gene as illustrated below.



Users can **hover** over any plot point to get quantitative information about the plot along. For example, when you hover over the first bar you should see popups describing **Thyroid cancer**, **52.55%** of samples are **Down Regulated** and **47.45%** are **Up Regulated**.

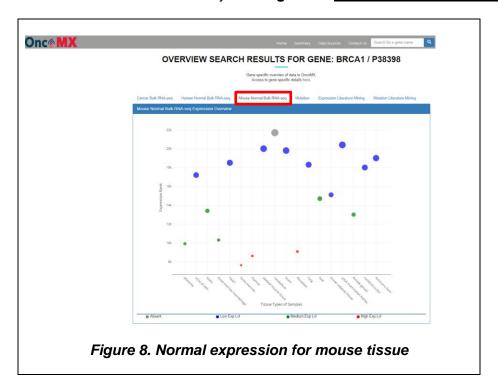
Step 3:

Click on <u>Human normal bulk RNA-seq</u> to view the graphical plot of normal tissue expression and the levels at which the searched gene is being expressed. The **silver** dots denote absent expression levels, **blue** denotes low expression, **green** denotes medium expression, and **red** high expression.

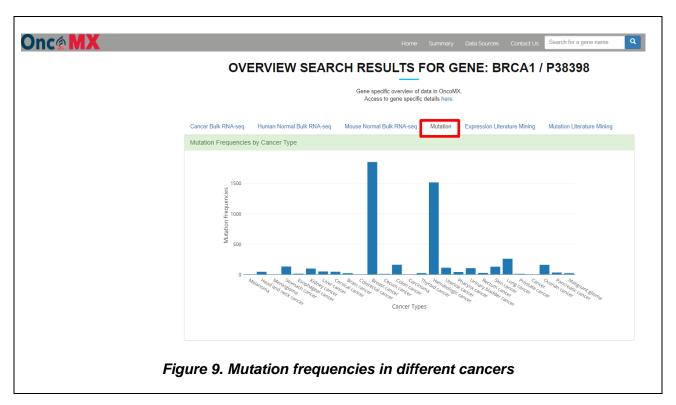


Step 4:

The user may also compare normal expression levels in different tissues in mouse data using the same criteria of scoring as the human data as illustrated below by **clicking** on the **Mouse normal RNA-seq** tab.

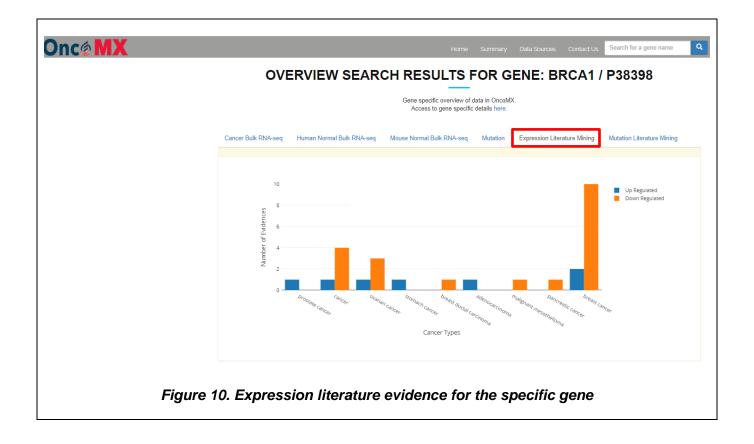


<u>Step 5:</u> **Click** on the <u>Mutation</u> tab to see the graphical representation of mutation frequencies for various cancer types for the BRCA1 gene.



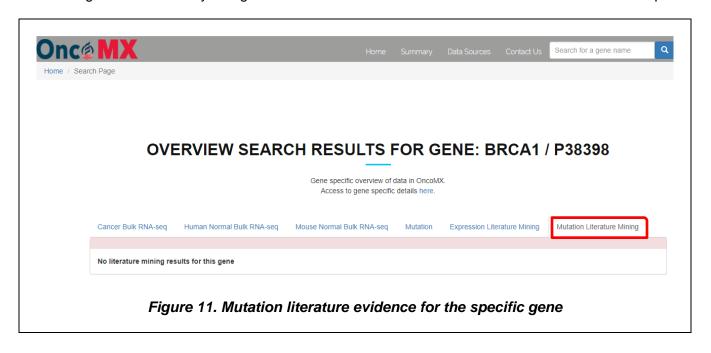
Step 6:

Click on the Expression Literature Mining tab to visualize the number of publications with evidence supporting the searched gene having some relationship between gene expression and each cancer type.



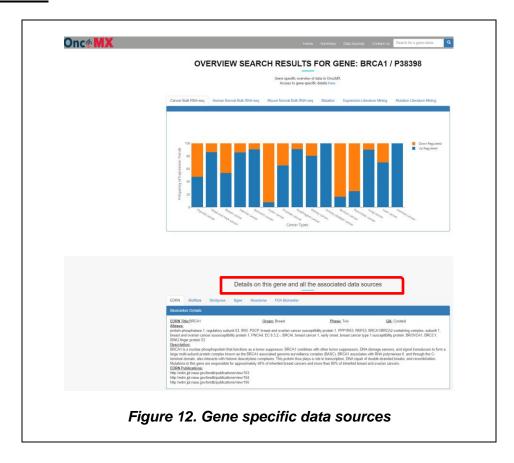
Step 7:

Click on the <u>Mutation Literature Mining</u> tab to visualize the number of publications reporting the searched gene to be mutated for each cancer type. Note, that there is currently no literature mutation data for this gene. The pilot dataset for mutation literature mining was exclusively for lung cancer. A new version of mutation literature mining results is actively being added to the database and should be available with the next update.

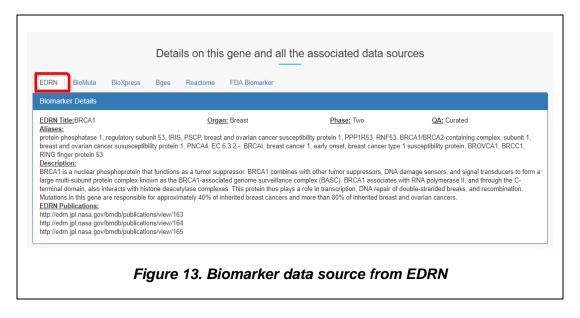


Step 8:

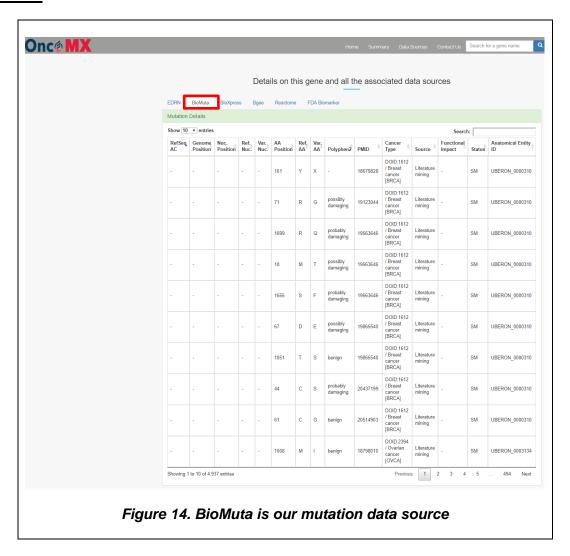
To further explore data sources associated with this gene, **scroll down** to the **Details on this gene and all associated data sources**.



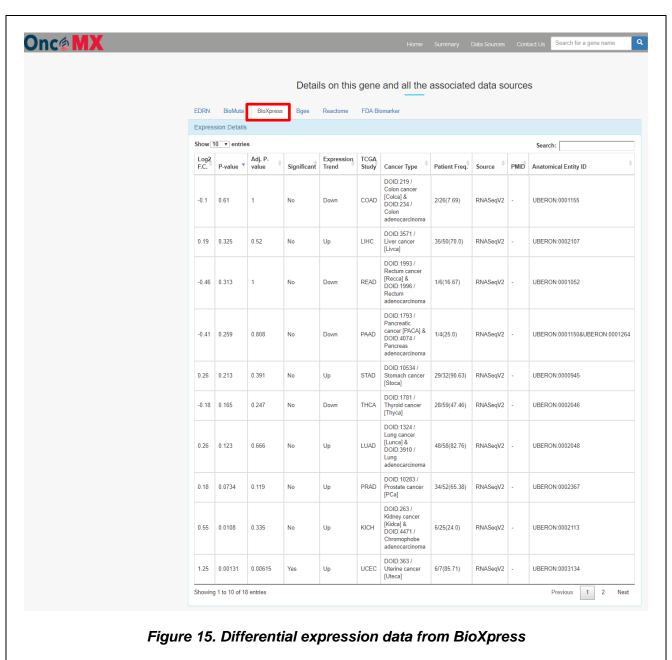
The first tab is <u>EDRN</u> where the users can view biomarker information on the BRCA1 gene retrieved from the Early Detection Research Network (EDRN) public biomarker record.



Step 9: Click on **BioMuta** to view the mutation source data.

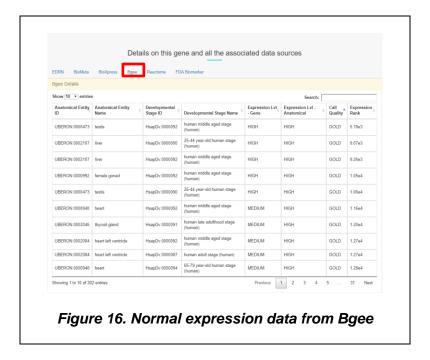


<u>Step 10:</u> **Click** on <u>**BioXpress**</u> to visualize the differential expression data for the queried gene.



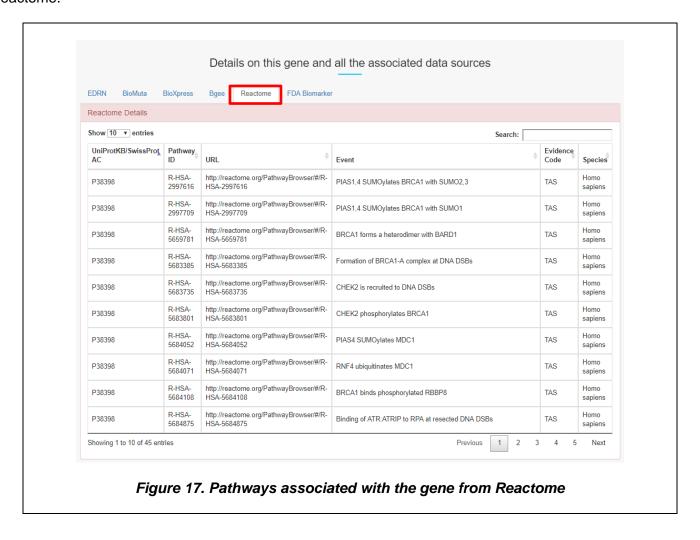
Step 11:

Click on Bgee to see normal expression data for human and mouse in a tabular format.



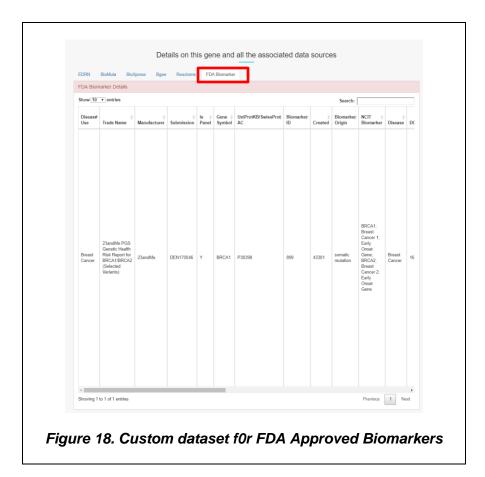
Step_12:

Click on <u>Reactome</u> to for a list and links to the pathways associated with this specific gene search provided by Reactome.



Step 13:

Click on the <u>FDA Biomarker</u> tab to see the custom generated dataset of FDA approved breast cancer biomarkers.



Contact and Availability

For more information, scroll all the way down from the main page to submit a contact request via webform.

For access to newest features, you can visit our beta site - https://beta.oncomx.org/.

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