CANCER GENOMICS CONSORTIUM

*Educating for Best Practices in Clinical Cancer Genomics*

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*Leading the search for tomorrow's cures*

# Jackson Laboratory Clinical Knowledgebase (JAX-CKB)

https://www.ncbi.nlm.nih.gov/pubmed/26772741

# Registering for Access

- https://www.jax.org/clinical-genomics/clinical-offerings/ckb
- Click on the link above and scroll down to green button that says “Access JAX-CKB”
- Fill out form and wait for email with link to access JAX-CKB
- JAX-CKB works best with Firefox and Chrome
- Register once and bookmark the sent URL at ckb.jax.org

# JAX-CKB Home Page

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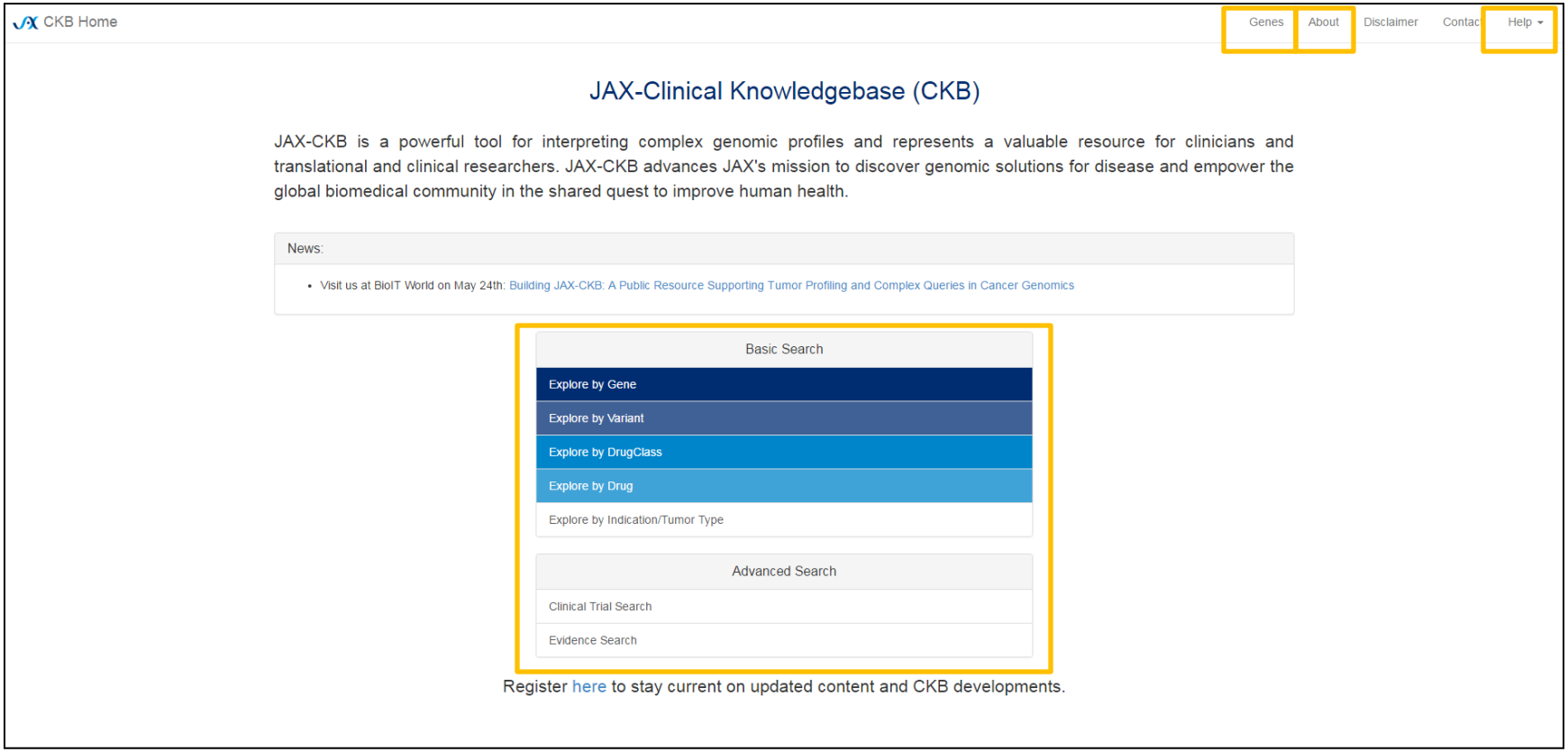

# Glossary of Terms

- https://ckb.jax.org/about/glossaryOfTerms
- Navigate to glossary of terms describing pertinent fields in knowledgebase data by selecting “Help” on top banner of Home page.
  - Glossary terms – gene, molecular profile, drug class, etc.
  - Evidence type
  - Protein Effect
  - Non-specific variants

# Evidence Type – directly from Glossary of

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- **Actionable**: clinical or preclinical data supporting a connection between a molecular profile and a drug response. The related response type may be sensitive or resistant.
- **Diagnostic**: connects a gene variant or category of variant to the diagnosis of a disease.
- **Emerging**: provides evidence for potential development of a gene variant as a future cancer therapy target.
- **Not Active**: indicates a particular therapy is no longer involved in any clinical trials and has no other available efficacy evidence.
- **Prognostic**: connects a gene variant or category of variant with disease outcome.
- **Risk Factor**: connects a germline gene variant or category of variant to the risk of disease onset.

# Protein Effect – from Glossary of Terms

- Effect on the intrinsic activity of the protein (not to downstream pathway events)
  - Gain / Loss of function
  - Gain / Loss of function – predicted
  - No effect
  - No effect - predicted

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# Non-Specific Variants – directly from Glossary of terms

- **act mut** - indicates that the variant results in a gain of protein function
- **amp** - indicates an increased number of copies of the gene
- **dec exp** - indicates decreased expression of the protein and/or mRNA
- **del** - indicates a deletion of the gene
- **fusion** - indicates a fusion of the gene, but the fusion partner is unspecified
- **inact mut** - indicates that the variant results in a loss of protein function
- **loss** - indicates loss of the gene, mRNA and protein
- **mutant** - indicates an unspecified mutation in the gene
- **negative** - indicates a lack of the gene, mRNA, and/or protein
- **over exp** - indicates overexpression of the protein and/or mRNA
- **positive** - indicates the presence of the gene, mRNA, and/or protein
- **rearrange** - indicates an unspecified rearrangement of the gene
- **wild-type** - indicates that no mutation has been detected within the gene

**These generic terms currently are only used when a data source does not mention a specific variant. For example, generic "act mut" does not include data on variants in a gene with a gain of function (GOF) activating mutation.

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# Tutorial

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- https://ckb.jax.org/about/tutorial

- **This is a great tutorial!**
  - Please use this tutorial to familiarize yourself with searching by gene, variant, drug, and indication as well as performing an Advanced Clinical Trials Search and Advanced Evidence Search.

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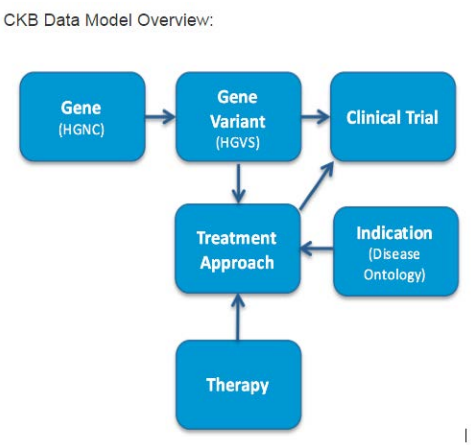
# About JAX-CKB




- Information on 82 known driver genes
  - Gene/Variant information
    - Diagnostic, Prognostic, and Predictive (therapy-related) information
    - Information on relevant clinical trials
      - Patient eligibility criteria
  - Data is curated daily with distinct curation methodology for classifying gene variants, types of evidence, and therapeutic response
- Commercial version of database has 900 genes and associated content.
  - Can be accessed through integration with 3rd party service provider.

# Genes in JAX-CKB

- https://ckb.jax.org/gene/grid
- Navigate to interactive gene grid by clicking on “Genes” on the top banner of the home page
- Navigate to any Gene Detail page by clicking on the corresponding gene button.

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ABL1 | AKT1 | ALK | APC | ASXL1 | ATM | ATRX | BCOR | BCORL1 | BRAF |
| BRCA1 | BRCA2 | CALR | CBL | CBLB | CBLC | CDH1 | CDKN2A | CEBPA | CSF1R |
| CSF3R | CTNNB1 | DNMT3A | EGFR | EML4 | ERBB2 | ERBB4 | ETV6 | EZH2 | FBXW7 |
| FGFR1 | FGFR2 | FGFR3 | FLT3 | FOXL2 | GATA1 | GATA2 | GNA11 | GNAQ | GNAS |
| HNF1A | HRAS | IDH1 | IDH2 | IKZF1 | JAK2 | JAK3 | KDM6A | KDR | KIT |
| KMT2A | KRAS | MAP2K1 | MET | MLH1 | MPL | MSH6 | MYD88 | NOTCH1 | NPM1 |
| NRAS | PDGFRA | PHF6 | PIK3CA | PTEN | PTPN11 | RAD21 | RB1 | RET | ROS1 |
| RUNX1 | SETBP1 | SF3B1 | SMAD4 | SMARCB1 | SMC3 | SMO | SRC | SRSF2 | STAG2 |
| STK11 | TET2 | TP53 | U2AF1 | VHL | ZRSR2 | | | | |

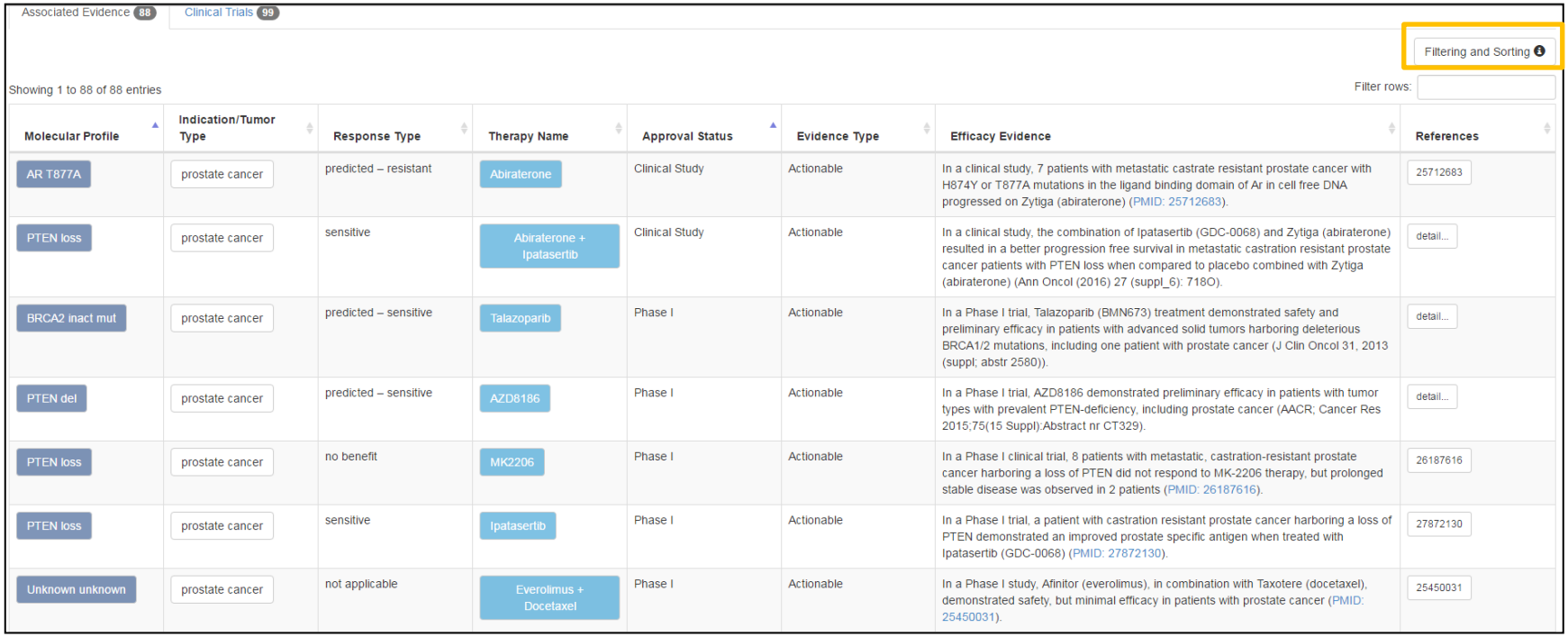
# Other search types – under "Help/FAQs" on Homepage

- Gene Fusions
  - First gene in fusion: type name twice separated by a space and followed by a dash "ETV6 ETV6 - "
  - Second gene in fusion: " - ALK"
- Copy Number Alterations
  - Search by gene name followed by either "amp" or "del"
- Expression data
  - Search by gene name followed by "dec exp" (decreased expression" or "over exp" (overexpression)

# Scenario #1

- You are wanting to know what genes to focus on while reviewing a whole genome microarray on an prostate cancer patient.
  - Search by indication = prostate cancer

# Search Results



Associated Evidence 88 | Clinical Trials 99

Filtering and Sorting

Showing 1 to 88 of 88 entries

Filter rows:

| Molecular Profile | Indication/Tumor Type | Response Type | Therapy Name | Approval Status | Evidence Type | Efficacy Evidence | References |
|---|---|---|---|---|---|---|---|
| AR T877A | prostate cancer | predicted – resistant | Abiraterone | Clinical Study | Actionable | In a clinical study, 7 patients with metastatic castrate resistant prostate cancer with H874Y or T877A mutations in the ligand binding domain of Ar in cell free DNA progressed on Zytiga (abiraterone) (PMID: 25712683). | 25712683 |
| PTEN loss | prostate cancer | sensitive | Abiraterone + Ipatasertib | Clinical Study | Actionable | In a clinical study, the combination of Ipatasertib (GDC-0068) and Zytiga (abiraterone) resulted in a better progression free survival in metastatic castration resistant prostate cancer patients with PTEN loss when compared to placebo combined with Zytiga (abiraterone) (Ann Oncol (2016) 27 (suppl_6): 718O). | detail... |
| BRCA2 inact mut | prostate cancer | predicted – sensitive | Talazoparib | Phase I | Actionable | In a Phase I trial, Talazoparib (BMN673) treatment demonstrated safety and preliminary efficacy in patients with advanced solid tumors harboring deleterious BRCA1/2 mutations, including one patient with prostate cancer (J Clin Oncol 31, 2013 (suppl; abstr 2580)). | detail... |
| PTEN del | prostate cancer | predicted – sensitive | AZD8186 | Phase I | Actionable | In a Phase I trial, AZD8186 demonstrated preliminary efficacy in patients with tumor types with prevalent PTEN-deficiency, including prostate cancer (AACR; Cancer Res 2015;75(15 Suppl):Abstract nr CT329). | detail... |
| PTEN loss | prostate cancer | no benefit | MK2206 | Phase I | Actionable | In a Phase I clinical trial, 8 patients with metastatic, castration-resistant prostate cancer harboring a loss of PTEN did not respond to MK-2206 therapy, but prolonged stable disease was observed in 2 patients (PMID: 26187616). | 26187616 |
| PTEN loss | prostate cancer | sensitive | Ipatasertib | Phase I | Actionable | In a Phase I trial, a patient with castration resistant prostate cancer harboring a loss of PTEN demonstrated an improved prostate specific antigen when treated with Ipatasertib (GDC-0068) (PMID: 27872130). | 27872130 |
| Unknown unknown | prostate cancer | not applicable | Everolimus + Docetaxel | Phase I | Actionable | In a Phase I study, Afinitor (everolimus), in combination with Taxotere (docetaxel), demonstrated safety, but minimal efficacy in patients with prostate cancer (PMID: 25450031). | 25450031 |

- Pertinent genes may be under Molecular profile
- Search yielded 88 evidence items and 99 clinical trials
- Far right column has links to PubMed and other details on the source of data
- Efficacy Evidence column provides summary of details on therapeutic response
- To capture child terms, use advanced search. (See next slide)
- Search results are in alphabetical order, but can be filtered.

# Genes identified through Search

- AR
- PTEN
- BRCA2
- ATM
- MET
- PIK3CA
- TP53
- KRAS
- AKT1
- NOTCH1

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Red = deleted in patient
Blue = amplified in patient

# Scenario #1 - B

- You would like to identify clinical trials that are currently recruiting for which your patient may be eligible.
  - Use Advanced Clinical Trial Search

# Advanced Clinical Trial

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- Gene Variant field
  - PTEN del
  - ATM del
  - KRAS amp
  - NOTE: Can only enter one at a time
- Indication/Tumor type
  - Prostate Cancer
- Look for directly associated clinical trials first, then at gene associated clinical trials if needed

# Advanced Clinical Trials

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- **PTEN del**
  - **1 directly associated clinical trial, RECRUITING**
  - 33 gene associated clinical trials
- **ATM del**
  - 0 directly associated clinical trials
  - 20 gene associated clinical trials
- **KRAS amp**
  - 0 directly associated clinical trials
  - 126 gene associated clinical trials

Advanced Clinical Trial Search Results

Search Parameters

Gene Variant: PTEN del (loss of function)

Drug:

Indication/Tumor Type(s): prostate cancer

Phase:

Directly Associated Clinical Trials 1 | Gene Associated Clinical Trials 33

Filtering and Sorting

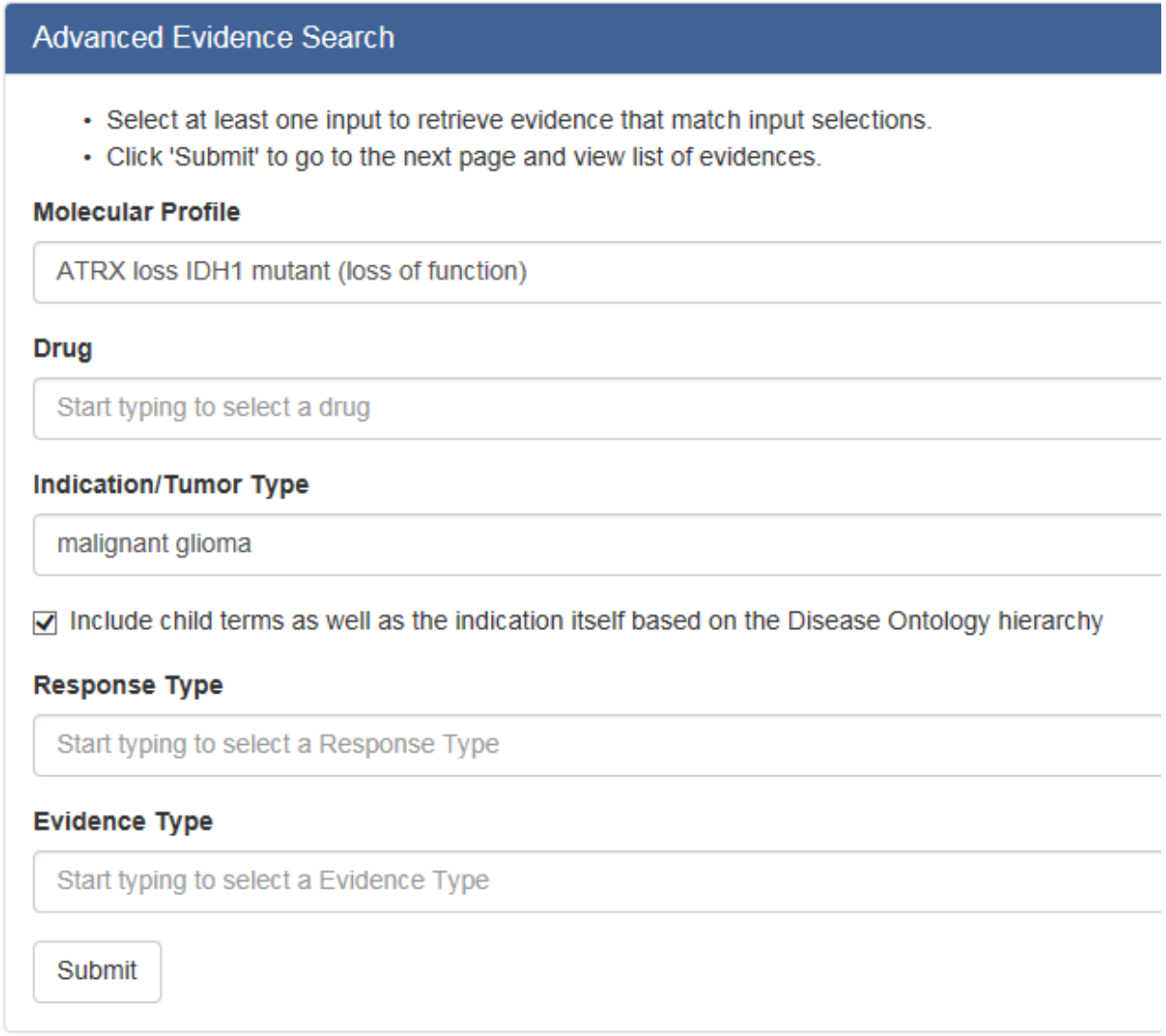
Showing 1 to 1 of 1 entries

Filter rows:

| Clinical Trial | Variant Requirement | Therapies | Phase | Title | Indication/Tumor Type(s) | Recruitment Status |
|---|---|---|---|---|---|---|
| NCT01884285 | yes | AZD8186 | Phase I | AZD8186 First Time In Patient Ascending Dose Study | triple-receptor negative breast cancer; non-small cell lung carcinoma; Advanced Solid Tumor; prostate cancer | Recruiting |

# Scenario #2

- You are researching the IDH mutant molecular profile in malignant glioma and are curious as to which drugs are involved in a clinical trial.
  - Advanced Evidence Search

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- Type "IDH1" or "ATRX" into the molecular profile field and/or select most relevant.
- Select malignant glioma from drop down
  - This particular drop down is from disease ontology
- Click "Submit"

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# Advanced Evidence Search Results

## Search Parameters

Includes child terms for disease

| | |
|---|---|
| Molecular Profile | ATRX loss IDH1 mutant |
| Drug | |
| Indication/Tumor Type(s) | malignant glioma, chordoid glioma, mixed glioma, mixed astrocytoma-ependymoma, mixed oligodendroglioma-astrocytoma, mixed astrocytoma-ependymoma-oligodendroglioma, malignant ependymoma, pediatric ependymoma, malignant adult ependymoma, astrocytoma, juvenile astrocytoma, gemistocytic astrocytoma, adult astrocytic tumour, adult infiltrating astrocytic neoplasm, pilomyxoid astrocytoma, pleomorphic xanthoastrocytoma, protoplasmic astrocytoma, astroblastoma, gliofibroma, grade III astrocytoma, glioblastoma multiforme, giant cell glioblastoma, glioblastoma proneural subtype, glioblastoma neural subtype, gliosarcoma, glioblastoma classical subtype, glioblastoma mesenchymal subtype, fibrillary astrocytoma, pilocytic astrocytoma, childhood pilocytic astrocytoma, juvenile pilocytic astrocytoma, oligodendroglioma, adult oligodendroglioma, childhood oligodendroglioma |
| Response Type | |
| Evidence Type | |

Associated Evidences 1

Filtering and Sorting

Showing 1 to 1 of 1 entries

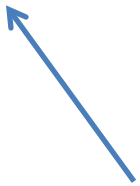
Filter rows:

| Molecular Profile | Indication/Tumor Type | Response Type | Therapy Name | Approval Status | Evidence Type | Efficacy Evidence | References |
|---|---|---|---|---|---|---|---|
| ATRX loss IDH1 mutant | malignant glioma | predicted – sensitive | Gemcitabine + Radiotherapy | Phase I | Actionable | In a Phase I trial, Gemzar (gemcitabine) plus radiation therapy resulted in median overall survival of 73.5 months in 7 high-grade glioma patients with IDH mutated, non-codeleted tumors with ATRX loss (PMID: 26853339). | 26853339 |

# Scenario #3

- You are making a list of pertinent cancer genes for your lab. How can JAX-CKB help?
  - Gene Grid
    - If you select all the buttons on the grid and click/drag Gene Grid, the entire list is copied over to whatever substrate you drag it into.
      - Genes will have active hyperlinks to their respective gene pages

| Genes |
|---|
| ABL1 |
| AKT1 |
| ALK |
| APC |
| ASXL1 |
| ATM |
| ATRX |
| BCOR |
| BCORL1 |
| BRAF |
| BRCA1 |
| BRCA2 |
| CALR |
| CBL |
| CBLB |
| CBLC |
| CDH1 |
| CDKN2A |
| CEBPA |
| CSF1R |
| CSF3R |
| CTNNB1 |
| DNMT3A |
| EGFR |
| EML4 |
| ERBB2 |
| ERBB4 |
| ETV6 |
| EZH2 |



Genes

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| ABL1 | AKT1 | ALK | APC | ASXL1 | ATM | ATRX | BCOR | BCORL1 | BRAF |
| BRCA1 | BRCA2 | CALR | CBL | CBLB | CBLC | CDH1 | CDKN2A | CEBPA | CSF1R |
| CSF3R | CTNNB1 | DNMT3A | EGFR | EML4 | ERBB2 | ERBB4 | ETV6 | EZH2 | FBXW7 |
| FGFR1 | FGFR2 | FGFR3 | FLT3 | FOXL2 | GATA1 | GATA2 | GNA11 | GNAQ | GNAS |
| HNF1A | HRAS | IDH1 | IDH2 | IKZF1 | JAK2 | JAK3 | KDM6A | KDR | KIT |
| KMT2A | KRAS | MAP2K1 | MET | MLH1 | MPL | MSH6 | MYD88 | NOTCH1 | NPM1 |
| NRAS | PDGFRA | PHF6 | PIK3CA | PTEN | PTPN11 | RAD21 | RB1 | RET | ROS1 |
| RUNX1 | SETBP1 | SF3B1 | SMAD4 | SMARCB1 | SMC3 | SMO | SRC | SRSF2 | STAG2 |
| STK11 | TET2 | TP53 | U2AF1 | VHL | ZRSR2 | | | | |

# Scenario #4

- Your lab has been involved with clinical trials and has had a recent publication. You would like to have this article incorporated into JAX-CKB.
  - Request curation by emailing ckbsupport@jax.org

# Citation of Use of JAX-CKB

- Podcast: http://media.aacc.org/CCJPodcasts/ClinChem_201603_Mockus.mp3
- https://www.ncbi.nlm.nih.gov/pubmed/27397723
- https://www.ncbi.nlm.nih.gov/pubmed/27503005
- https://www.ncbi.nlm.nih.gov/pubmed/27503005
- https://www.ncbi.nlm.nih.gov/pubmed/26607725

# Contacting JAX-CKB

- ckbsupport@jax.org

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