Jackson Laboratory Clinical Knowledgebase (JAX-CKB)

Registering for Access

- [https://www.jax.org/clinical-genomics/clinical-offerings/ckb](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-C KB Home Page

JAX-C Clinical Knowledgebase (CKB)

JAX-CKB is a powerful tool for interpreting complex genomic profiles and represents a valuable resource for clinicians and translational and clinical researchers. JAX-CKB advances JAX’s mission to discover genomic solutions for disease and empower the global biomedical community in the shared quest to improve human health.

News:
- Visit us at BioIT World on May 24th: Building JAX-CKB: A Public Resource Supporting Tumor Profiling and Complex Queries in Cancer Genomics

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<td>Explore by Drugcases</td>
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<td>Explore by Drug</td>
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Register [here](#) to stay current on updated content and CKB developments.
Glossary of Terms

- [https://ckb.jax.org/about/glossaryOfTerms](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

- **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
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.**
**Tutorial**

- [https://ckb.jax.org/about/tutorial](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.
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.

<table>
<thead>
<tr>
<th>ABL1</th>
<th>AKT1</th>
<th>ALK</th>
<th>APC</th>
<th>ASXL1</th>
<th>ATM</th>
<th>ATRX</th>
<th>BCOR</th>
<th>BCORL1</th>
<th>BRF1</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRCA1</td>
<td>BRCA2</td>
<td>CALR</td>
<td>CBL</td>
<td>CBLB</td>
<td>CBLC</td>
<td>CDH1</td>
<td>CDKN2A</td>
<td>CEBPA</td>
<td>CSF1R</td>
</tr>
<tr>
<td>CSF3R</td>
<td>CTNNB1</td>
<td>DNMT3A</td>
<td>EGFR</td>
<td>EML4</td>
<td>ERBB2</td>
<td>ERBB4</td>
<td>ETV6</td>
<td>EZH2</td>
<td>FBXW7</td>
</tr>
<tr>
<td>FGFR1</td>
<td>FGFR2</td>
<td>FGFR3</td>
<td>FLT3</td>
<td>FOXO1</td>
<td>GATA1</td>
<td>GATA2</td>
<td>GNA11</td>
<td>GNAN</td>
<td>GNAS</td>
</tr>
<tr>
<td>HNF1A</td>
<td>HRAS</td>
<td>IDH1</td>
<td>IDH2</td>
<td>IKZF1</td>
<td>JAK2</td>
<td>JAK3</td>
<td>KDM6A</td>
<td>KDR</td>
<td>KIT</td>
</tr>
<tr>
<td>KMT2A</td>
<td>KRAS</td>
<td>MAP2K1</td>
<td>MET</td>
<td>MLH1</td>
<td>MPL</td>
<td>MSH6</td>
<td>MYD88</td>
<td>NOTCH1</td>
<td>NPM1</td>
</tr>
<tr>
<td>NRAS</td>
<td>PDCD1</td>
<td>PHF6</td>
<td>PIK3CA</td>
<td>PTEN</td>
<td>PTPN11</td>
<td>RAF1</td>
<td>RB1</td>
<td>RET</td>
<td>ROS1</td>
</tr>
<tr>
<td>RUNX1</td>
<td>SETBP1</td>
<td>SF3B1</td>
<td>SMAD4</td>
<td>SMARCB1</td>
<td>SMC3</td>
<td>SMO</td>
<td>SRC</td>
<td>SRCF1</td>
<td>STAG2</td>
</tr>
<tr>
<td>STK11</td>
<td>TET2</td>
<td>TP53</td>
<td>U2AF1</td>
<td>VHL</td>
<td>ZRSR2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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 a prostate cancer patient.
  – Search by indication = prostate cancer
### Search Results

<table>
<thead>
<tr>
<th>Associated Evidence</th>
<th>Clinical Trials</th>
</tr>
</thead>
</table>

#### Molecular Profile

<table>
<thead>
<tr>
<th>Indication/Tumor Type</th>
<th>Response Type</th>
<th>Therapy Name</th>
<th>Approval Status</th>
<th>Evidence Type</th>
<th>Efficacy Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ar T877A</td>
<td>prostate cancer</td>
<td>predicted – resistant</td>
<td>Abiraterone</td>
<td>Clinical Study</td>
<td>Actionable</td>
</tr>
<tr>
<td>PTEN loss</td>
<td>prostate cancer</td>
<td>sensitive</td>
<td>Abiraterone + Ipatasertib</td>
<td>Clinical Study</td>
<td>Actionable</td>
</tr>
<tr>
<td>BRCA2 inact mut</td>
<td>prostate cancer</td>
<td>predicted – sensitive</td>
<td>Talazoparib</td>
<td>Phase I</td>
<td>Actionable</td>
</tr>
<tr>
<td>PTEN del</td>
<td>prostate cancer</td>
<td>predicted – sensitive</td>
<td>AZD8166</td>
<td>Phase I</td>
<td>Actionable</td>
</tr>
<tr>
<td>PTEN loss</td>
<td>prostate cancer</td>
<td>no benefit</td>
<td>MK2206</td>
<td>Phase I</td>
<td>Actionable</td>
</tr>
<tr>
<td>PTEN loss</td>
<td>prostate cancer</td>
<td>sensitive</td>
<td>Ipatasertib</td>
<td>Phase I</td>
<td>Actionable</td>
</tr>
<tr>
<td>Unknown unknown</td>
<td>prostate cancer</td>
<td>not applicable</td>
<td>Everolimus + Docetaxel</td>
<td>Phase I</td>
<td>Actionable</td>
</tr>
</tbody>
</table>

#### Efficacy Evidence

- 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

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

- 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

- **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

- **Gene Variant**: PTEN del
- **Drug**:
  - Indication/Tumor Type(s): prostate cancer
- **Phase**:
  - Directly Associated Clinical Trial:
  - Gene Associated Clinical Trial: 33

Showing 1 to 1 of 1 entries

**Clinical Trial**: NCT01994285
**Variant Requirement**: yes
**Therapies**: AZD6166
**Phase**: Phase 1
**Title**: AZD6166 First Time In Patient Ascending Dose Study
**Indications/Tumor Type(s)**: triple-negative metastatic breast cancer, non-small-cell lung carcinoma, Advanced Solid Tumor, prostate cancer
**Recruitment Status**: 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
To use the Advanced Evidence Search, follow these steps:

1. **Molecular Profile**
   - Type “IDH1” or “ATRX” into the molecular profile field and/or select most relevant.

2. **Indication/Tumor Type**
   - Select malignant glioma from the drop-down list.
     - This particular drop-down is from the Disease Ontology hierarchy.

3. **Response Type** and **Evidence Type**
   - Start typing to select a Response Type and Evidence Type.

4. **Submit**
   - Click “Submit” to proceed.
### Advanced Evidence Search Results

#### Search Parameters

<table>
<thead>
<tr>
<th>Molecular Profile</th>
<th>ATRX loss IDH1 mutant</th>
</tr>
</thead>
</table>

#### 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 | glioblastoma | grade III astrocytoma | glioblastoma multiforme | giant cell glioblastoma | glioblastoma proneural subtype | glioblastoma neural subtype | gliosarcoma | glioblastoma classical subtype | glioblastoma mesenchymal subtype | fibrillary astrocytoma | picrocytic astrocytoma | childhood picrocytic astrocytoma | juvenile picrocytic astrocytoma | oligodendroglioma | adult oligodendroglioma | childhood oligodendroglioma |
|-------------------------|-------------------|-----------------|-------------|-----------------------------|-------------------------------------|-------------------------------------------|--------------------|----------------------|-----------------------------|-------------|---------------------|----------------------|------------------------|---------------------------|------------------------|------------------------|------------------------|----------------|----------------------|----------------------|------------------------|------------------------|------------------------|------------------------|-----------------|----------------------|----------------------|------------------------|------------------------|------------------------|------------------------|

#### Response Type

<table>
<thead>
<tr>
<th>Evidence Type</th>
<th>Associated Evidences</th>
</tr>
</thead>
</table>

#### Showing 1 to 1 entries

<table>
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<tr>
<th>Molecular Profile</th>
<th>Indication/Tumor Type</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ATRX loss IDH1 mutant</td>
<td>malignant glioma</td>
<td>predicted – sensitive</td>
<td>Gemcitabine + Radiotherapy</td>
<td>Phase I</td>
<td>Actionable</td>
<td>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: 29533339)</td>
</tr>
</tbody>
</table>

[29533339]
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
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-C KB

- Podcast:
  http://media.aacc.org/CCJPodcasts/ClinChem_201603_Mockus.mp3
Contacting JAX-CKB

- ckbsupport@jax.org