



# JAX Clinical Knowledgebase (JAX-CKB) Tutorial

## CKB CORE™

<https://ckbhome.jax.org>

# Getting Started

This button returns you to the home page .

## The Clinical Knowledgebase (CKB) Powered by The Jackson Laboratory

This tab brings you to a clickable display of the genes available in CKB CORE™.

This tab brings you to a list of associated CKB help documents

CKB is a dynamic digital resource for interpreting complex cancer genomic profiles in the context of protein impact, therapies, and clinical trials. CKB CORE is the public access version we have been providing to the community since 2016. CKB CORE contains all the content associated with 50 genes that are commonly found on cancer hotspot panels. New and updated content is pushed out daily and viewable genes are available on a quarterly rotating schedule.

Basic Search

Explore by Gene

Explore by Variant

Explore by DrugClass - Available in CKB BOOST

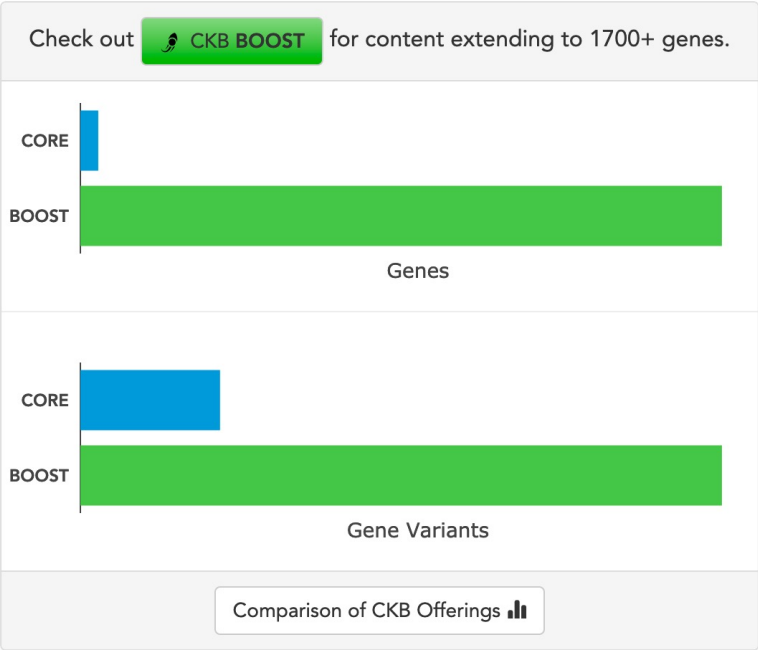
Explore by Drug - Available in CKB BOOST

Explore by Indication/Tumor Type - Available in CKB BOOST

Advanced Search

Clinical Trial Search - Available in CKB BOOST

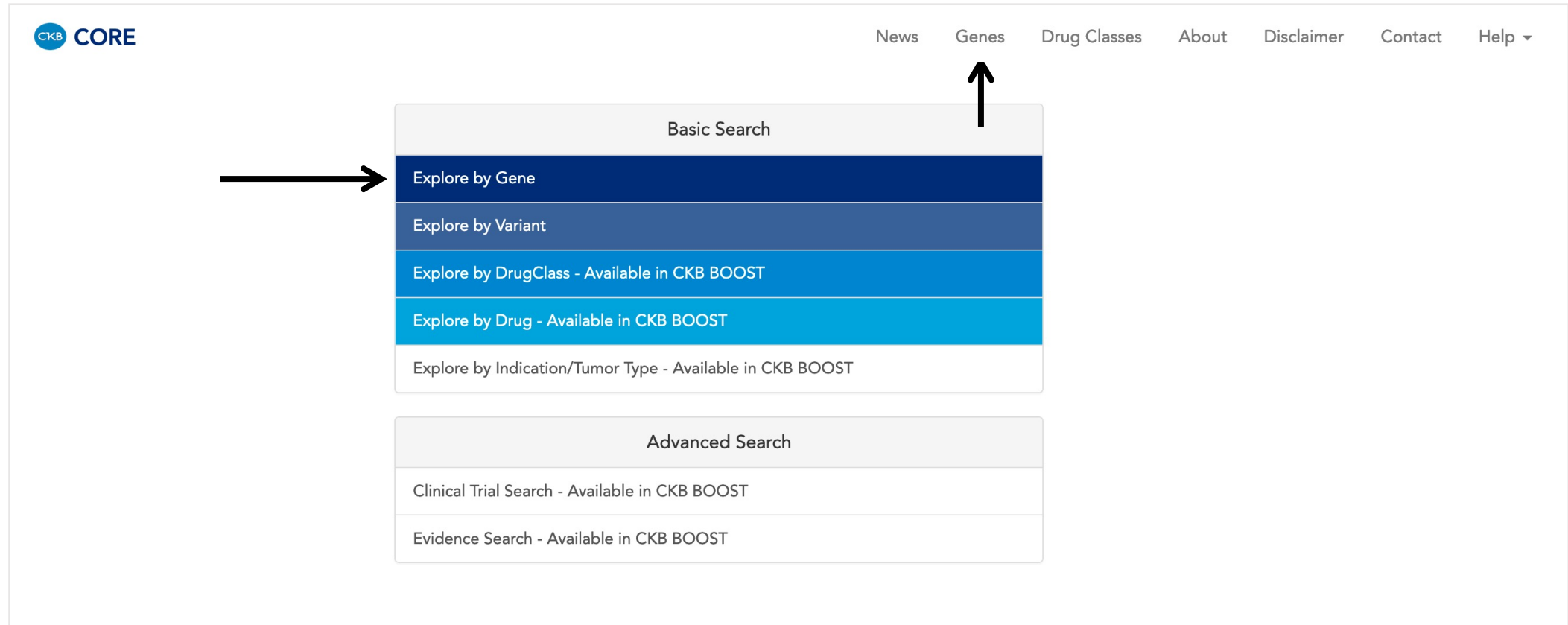
Evidence Search - Available in CKB BOOST



CKB-CORE™ can be searched on through gene and gene variant. Additional basic searches and advanced searches require a subscription to CKB BOOST™.

Visual shows the difference in gene and gene variant counts for CORE vs BOOST.

# Explore By Gene



- Clicking on the “Explore by Gene” button will bring you to a page where you can search for content related to 50 selected genes.
- Clicking on the “Genes” link in the toolbar will bring you to a clickable list of genes with available content.

Explore By Gene

## Find by Gene

- Start typing a gene name to display gene.
- Select **one** gene and click 'Submit' to go to the next page.
- Or search for a gene via the **Gene Grid**

**Gene Symbol**

Start typing to select a gene

BR|

ABR | MDB

ACTB | BRWS1 | PS1TP5BP1

BRCA1 | BRCA1 | BRCC1 | BROVCA1 | FANCS | IRIS | PNCA4 | PPP1R53 | PSCP | RNF53

BRAF | B-raf | B-RAF1 | BRAF1 | NS7 | RAFB1

BRCA2 | BRCC2 | BROVCA2 | FACD | FAD | FAD1 | FANCD | FANCD1 | GLM3 | PNCA2 | XRCC11

BRDT | BRD6 | CT9 | SPGF21

ZFP36L1 | Berg36 | BRF1 | cMG1 | ERF-1 | ERF1 | RNF162B | TIS11B

**BRAF | B-raf | B-RAF1 | BRAF1 | NS7 | RAFB1**

**Gene Description:**

BRAF, serine/threonine-protein kinase B-raf, is a member of the Raf family of serine/threonine protein kinases, which signals through the MAP kinase pathway to regulate cell proliferation and cell growth (PMID: 24737949, PMID: 29540830). BRAF mutations and fusions have been identified in a variety of cancers, including, colorectal (PMID: 30122982), lung (PMID: 29729495), thyroid (PMID: 12970315), and melanoma (PMID: 24737949), and a number of mutations have also been demonstrated to confer drug resistance (PMID: 27478040).

Typing in the search box will trigger a drop-down list of genes. Genes in CKB are given HGNC approved names, but associated synonyms are also available for searching. **Click** on the desired gene name to select for searching. This will bring you to the “Gene Detail Page” for the selected gene.

# Explore By Gene

CKB CORE

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Request Content

## Gene Detail

Gene Symbol

BRAF

Synonyms

B-raf | B-RAF1 | BRAF1 | NS7 | RAFB1

Gene Description

BRAF, serine/threonine-protein kinase B-raf, is a member of the Raf family of serine/threonine protein kinases, which signals through the MAP kinase pathway to regulate cell proliferation and cell growth (PMID: 24737949, PMID: 29540830). BRAF mutations and fusions have been identified in a variety of cancers, including, colorectal (PMID: 30122982), lung (PMID: 29729495), thyroid (PMID: 12970315), and melanoma (PMID: 24737949), and a number of mutations have also been demonstrated to confer drug resistance (PMID: 27478040).

NCBI Gene ID	Chromosome	Map Location	Canonical Transcript	Gene Role
673	7	7q34	NM_004333	Oncogene (PMID: 30606230)

Gene Variants 278

Category Variants 29

Molecular Profiles 380

Gene Level Evidence 1021

Filtering and Sorting

Filter rows:

Showing 1 to 278 of 278 entries

Variant	Impact	Protein Effect	Variant Description	Associated with drug Resistance
N20T	missense	unknown	BRAF N20T does not lie within any known functional domains of the Braf protein (UniProt.org). N20T has been identified in sequencing studies (PMID: 29106415), but has not been biochemically characterized and therefore, its effect on Braf protein function is unknown (PubMed, Apr 2021).	
S36A	missense	unknown	BRAF S36A does not lie within any known functional domains of the Braf protein (UniProt.org). S36A has not been characterized in the scientific literature and therefore, its effect on Braf protein function is unknown (PubMed, Jun 2021).	

Link out to PubMed through PMIDs

Link out to NCBI

Count of related annotations

Text Filtering

- The header of the page contains data relevant to the gene, as well as a link out to the NCBI Gene page (Entrez ID), chromosome and map location, the canonical transcript, and its role in cancer.
- Below, there are 4 tabs related to different areas of content:
  - The 'Gene Variants' tab lists all annotated gene variants associated with the selected gene.
  - The 'Category Variants' tab lists all annotated category variants associated with the selected gene.
  - The 'Molecular Profiles' tab contains all molecular profiles (which contain one or more gene variants) associated with the selected gene.
  - The 'Gene Level' Evidence tab lists all annotated evidence associated with the selected gene.
- All pages also incorporate filtering and sorting capability to enable easy content searching.

# Explore By Gene

## Gene Variant Tab

Gene Variants 281 Category Variants 32 Molecular Profiles 383 Gene Level Evidence 1031

Filtering and Sorting ⓘ

Filter rows: 600

Showing 1 to 25 of 25 entries (filtered from 281 total entries)

Variant	Impact	Protein Effect	Variant Description	Associated with drug Resistance
L514V	missense	gain of function - predicted	BRAF L514V lies within the protein kinase domain of the Braf protein (UniProt.org). L514V is predicted to lead to a gain of Braf function as indicated by moderate increase of Mek and Erk phosphorylation in culture, enhanced dimerization when expressed in cis with BRAF V600E, and is associated with resistance to Raf inhibitors (PMID: 29880583).	Y
T529I	missense	unknown	BRAF T529I is a gatekeeper mutation that lies within the protein kinase domain of the Braf protein (PMID: 20538618). T529I has been demonstrated to confer resistance to Raf inhibitors in the context of BRAF V600E (PMID: 20538618), but has not been biochemically characterized and therefore, its effect on Braf protein function is unknown (PubMed, Dec 2020).	Y
D594_T599dup	duplication	gain of function	BRAF D594_T599dup (also referred to as T599_V600insDFGLAT) results in the insertion of six amino acids in the protein kinase domain of the Braf protein between amino acids 599 and 600 (UniProt.org). BRAF D594_T599dup results in increased colony formation and downstream Mek and Erk activation in cultured cells (PMID: 17297294).	
G596R	missense	loss of function - predicted	BRAF G596R lies within the protein kinase domain of the Braf protein, within the DFG motif (PMID: 19735675). G596R results in impaired Braf kinase activity and decreased Mek and Erk phosphorylation, including in the presence of BRAF V600E, is not transforming in culture and does not promote tumor formation in mouse models, but results in activation of Erk in the presence of CRAF (PMID: 19735675, PMID: 28783719), however, in another study demonstrates similar cell proliferation and viability levels to wild-type Braf (PMID: 29533785), and is predicted to confer a loss of function to the Braf protein.	
T599A	missense	loss of function	BRAF T599A lies within the protein kinase domain of the Braf protein (UniProt.org). T599A does not result in increased MEK or ERK phosphorylation and does not transactivate CRAF (PMID: 22506009), and demonstrates decreased transformation ability compared to wild-type Braf in cell culture (PMID: 29533785).	

You can filter on any relevant text here. In this example, we've filtered on 600, which will restrict the display to variants containing "600"

Variants associated with drug resistance will have 'Y' in this column.

The **Gene Variant** tab lists gene variants for the selected gene, their impact on the protein (corresponding to variant type), their effect on the intrinsic activity of the protein, and an annotated description. Links in blue will navigate to outside content. Content can be sorted or filtered. Clicking on the blue "gene variant" buttons will bring you to the Gene Variant Detail Page.

# Explore By Gene

Gene Variants 281 Category Variants 32 Molecular Profiles 383 Gene Level Evidence 1031

Filtering and Sorting ⓘ

Filter rows:

Showing 1 to 32 of 32 entries

Variant	Impact	Protein Effect	Variant Description	Associated with drug Resistance
class 1	unknown	gain of function	BRAF Class 1 variants are BRAF variants that activate BRAF and downstream signaling in a dimer-independent, RAS-independent manner (PMID: 28783719, PMID: 26343582).	
class 2	unknown	gain of function	BRAF Class 2 variants are BRAF variants that activate BRAF and downstream signaling in a dimer-dependent, RAS-independent manner (PMID: 28783719, PMID: 26343582).	
class 3	unknown	loss of function	BRAF Class 3 variants are BRAF variants that demonstrate low or no BRAF kinase activity, but activate downstream signaling through CRAF activation, in a dimer-dependent, RAS-dependent manner (PMID: 28783719).	
T241X	missense	unknown	BRAF T241X indicates any Braf missense mutation that results in replacement of the threonine (T) at amino acid 241 by a different amino acid.	
Q257X	missense	unknown	BRAF Q257X indicates any Braf missense mutation that results in replacement of the glutamine (Q) at amino acid 257 by a different amino acid.	
P367X	missense	unknown	BRAF P367X indicates any Braf missense mutation that results in replacement of the proline (P) at amino acid 367 by a different amino acid.	
P403fs	frameshift	loss of function - predicted	BRAF P403fs results in a change in the amino acid sequence of the Braf protein beginning at aa 403 of 766, likely resulting in premature truncation of the functional protein (UniProt.org). Due to the loss of the protein kinase domain (UniProt.org), P403fs is predicted to lead to a loss of Braf protein function.	
R462X	missense	unknown	BRAF R462X indicates any Braf missense mutation that results in replacement of the arginine (R) at amino acid 462 by a different amino acid.	

The **Category Variants** tab displays all category variants associated with the selected gene. Category variants can be classified as functional and/or positional. Functional category variants include act mut and inact mut. Examples of positional variants include exon, codon, and short form frameshifts. Category variants can include member variants and can be used to identify relevant efficacy evidence. For more information about category variants, click [here](#).

# Explore By Gene

Gene Variants 281   Category Variants 32   **Molecular Profiles 383**   Gene Level Evidence 1031

Filtering and Sorting ⓘ

Filter rows:

Showing 1 to 383 of 383 entries

Molecular Profile	Protein Effect	Treatment Approaches
BRAF A598_T599insARC	gain of function - predicted	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120
BRAF A598_T599insV	gain of function	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120
BRAF A598V	gain of function - predicted	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120
BRAF A728V	gain of function	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120
BRAF act mut	gain of function	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120
BRAF D594_T599dup	gain of function	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120
BRAF E586K	gain of function	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120
BRAF F247L	gain of function	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120
BRAF F468C	gain of function	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120
BRAF G464E	gain of function	MEK inhibitor (Pan)   MEK1 Inhibitor   MEK2 Inhibitor   LY3009120

The **Molecular Profile** tab displays all molecular profiles associated with the selected gene, which can contain one or more gene variants. If appropriate, any related treatment approaches are listed. Treatment approaches are either Drug Classes or individual Therapies that have been assigned to variants based on evidence from the literature. Clicking on these buttons will bring you to the “Profile Treatment Approach Detail” page.

# Explore By Gene

Gene Variants 281   Category Variants 32   Molecular Profiles 383   **Gene Level Evidence 1031**

**Gene Level Evidence Tab**

Filtering and Sorting ⓘ

Filter rows: V600E

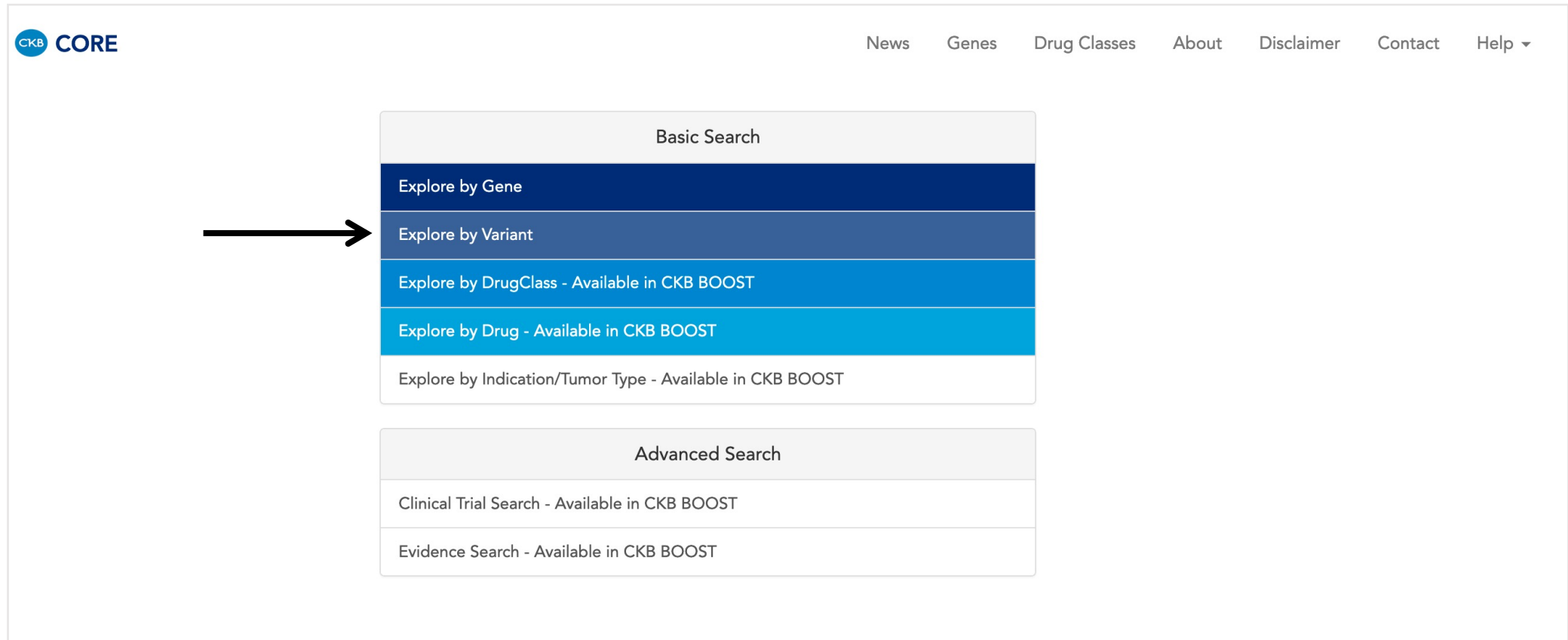
Showing 1 to 552 of 552 entries (filtered from 1,031 total entries)

Molecular Profile	Indication/Tumor Type	Response Type	Therapy Name	Approval Status	Evidence Type	Efficacy Evidence	References
BRAF V600E	melanoma	sensitive	Dabrafenib	FDA approved - On Companion Diagnostic	Actionable	In a Phase III clinical trial (BREAK-3) that supported FDA approval, Tafinlar (dabrafenib) improved median progression-free survival compared to Deticene (dacarbazine) (5.1 vs 2.7 months, HR=0.3, p<0.0001) in patients with BRAF V600E positive melanoma (PMID: <a href="#">22735384</a> ; NCT01227889).	<a href="#">detail...</a> 22735384
BRAF V600E	melanoma	sensitive	Vemurafenib	FDA approved - On Companion Diagnostic	Actionable	In a Phase III trial (BRIM-3) that supported FDA approval, Zelboraf (vemurafenib), as compared to Deticene (dacarbazine), resulted in an improved overall survival (OS) (13.6 vs 9.7 months, HR=0.81, p=0.03) in patients with BRAF V600E-positive metastatic melanoma, with estimated OS rates of 56%, 30%, 21%, and 17% at 1, 2, 3, and 4 years, respectively (PMID: <a href="#">28961848</a> , PMID: <a href="#">21639808</a> ; NCT01006980), and BRAF V600E is included on the companion diagnostic (FDA.gov).	<a href="#">detail...</a> 28961848 <a href="#">detail...</a> 21639808
BRAF V600E	melanoma	sensitive	Dabrafenib + Trametinib	FDA approved - On Companion Diagnostic	Actionable	In a Phase III trial (COMBI-v) that supported FDA approval, the combination of Tafinlar (dabrafenib) and Mekinist (trametinib) resulted in an improved overall survival rate at 12 months (72% vs 65%, HR=0.69, p=0.005), median progression-free survival (11.4 vs 7.3 months, HR=0.56, p<0.001), and objective response rate (64% vs 51%, p<0.001) compared to Zelboraf (vemurafenib) in melanoma patients harboring BRAF V600E or V600K (PMID: <a href="#">25399551</a> ; NCT01597908).	<a href="#">detail...</a> 25399551
BRAF V600E	colorectal cancer	sensitive	Cetuximab + Encorafenib	FDA approved - On Companion	Actionable	In a Phase III (BEACON CRC) trial that supported FDA approval, Braftovi (encorafenib) and Erbitux (cetuximab) combination treatment	<a href="#">detail...</a>

The **Gene Level Evidence** tab displays all annotated evidence associated with gene variants in the selected gene. Links in blue go out to PubMed for the associated references.

There are multiple 'Evidence Types'. The majority are "Actionable", meaning there is an association between a gene variant and therapy. Other evidence types are: "Prognostic" (variant association with disease outcome), "Diagnostic" (variant association with disease diagnosis), "Risk Factor" (germline variant association with risk of disease onset), and "Emerging" (variant as a potential therapeutic target).

# Explore By Gene Variant



- Clicking on the “Explore by Variant” button will bring you to a page where you can search for content related to a gene variant.

# Explore By Gene Variant

## Find by Gene Variant

- Start typing a gene variant name to display gene variant.
- Select **one** gene variant and click 'Submit' to go to the next page.

### Gene Variant

Start typing to select one or more variants

BRAF V600E



**BRAF V600E (gain of function)**

BRAF V600E/K (gain of function)

### BRAF V600E (gain of function)

#### Gene Description:

BRAF, serine/threonine-protein kinase B-raf, is a member of the Raf family of serine/threonine protein kinases, which signals through the MAP kinase pathway to regulate cell proliferation and cell growth (PMID: 24737949, PMID: 29540830). BRAF mutations and fusions have been identified in a variety of cancers, including, colorectal (PMID: 30122982), lung (PMID: 29729495), thyroid (PMID: 12970315), and melanoma (PMID: 24737949), and a number of mutations have also been demonstrated to confer drug resistance (PMID: 27478040).

#### Gene Variant Description:

BRAF V600E (previously reported as V599E) lies within the activation segment of the kinase domain of the Braf protein (PMID: 15035987). V600E confers a gain of function to the Braf protein as demonstrated by increased Braf kinase activity, downstream signaling, and the ability to transform cells in culture (PMID: 15035987, PMID: 29533785).

Typing in the search box will trigger a drop-down list of gene variants. Gene variants in CKB follow HGVS nomenclature. **Click** on the desired gene variant to select for searching. This will bring you to the “Molecular Profile Detail Page” for the selected gene variant.

# Explore By Gene Variant

CKB

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Molecular Profile Detail

Request Content

Profile Name

BRAF V600E

Gene Variant Detail

BRAF V600E (gain of function)

BRAF V600E (previously reported as V599E) lies within the activation segment of the kinase domain of the Braf protein (PMID: 15035987). V600E confers a gain of function to the Braf protein as demonstrated by increased Braf kinase activity, downstream signaling, and the ability to transform cells in culture (PMID: 15035987, PMID: 29533785).

Relevant Treatment Approaches

BRAF Inhibitor

or (Pan)

Variant Level Evidence 323

Complex Molecular Profile Evidence 186

Extended Evidence 128

Gene Level Evidence 1031

Treatment Approach Evidence 145

Variant Associated Clinical Trials 87

Gene Associated Clinical Trials 309

Filtering and Sorting

Filter rows:

Showing 1 to 323 of 323 entries

Molecular Profile	Indication/Tumor Type	Response Type	Relevant Treatment Approaches	Therapy Name	Approval Status	Evidence Type	Efficacy Evidence	References
BRAF V600E	colorectal cancer	sensitive	BRAF Inhibitor	Cetuximab + Encorafenib	FDA approved - On Companion Diagnostic	Actionable	In a Phase III (BEACON CRC) trial that supported FDA approval, Braftovi (encorafenib) and Erbitux (cetuximab) combination treatment (n=113) resulted in improved median overall survival (8.4 vs 5.4 months, HR=0.60, p<0.001), confirmed response rate (20% vs 2%, p<0.001), and median progression-free survival (4.2 vs 1.5 months, HR=0.40, p<0.001) compared to control (n=107) in patients with metastatic colorectal cancer.	<div>detail...</div> <div>31566309</div>

- To view the gene variant description, hover over the variant button next to Gene Variant Detail in the header.
- Below, there are 7 tabs related to different areas of content:
  - The 'Variant Level Evidence' tab lists all annotated evidence that includes only the gene variant in the molecular profile.
  - The 'Complex Molecular Profile Evidence' tab lists all annotated evidence that includes the gene variant plus one or more other variants in the molecular profile.
  - The 'Extended Evidence' tab lists all annotated evidence that includes the category variant(s) in which the gene variant is a member.
  - The 'Gene Level Evidence' tab lists all annotated evidence associated with the gene.
  - The 'Treatment Approach Evidence' tab lists all the annotated evidence related to the Relevant Treatment Approaches listed in the header under Gene Variant Detail.
  - The 'Variant Associated Clinical Trials' tab lists all the trials that include the gene variant as a variant requirement.
  - The 'Gene Associated Clinical Trials' tab lists all the trials that include a any variant in the associated gene.
- All pages also incorporate filtering and sorting capability to enable easy content searching.

# Explore By Gene Variant

Variant Level Evidence 323

Complex Molecular Profile Evidence 186

Extended Evidence 128

Gene Level Evidence 1031

Treatment Approach Evidence 145

Variant Associated Clinical Trials 87

Gene Associated Clinical Trials 309

## Variant Associated Clinical Trials

Filtering and Sorting ⓘ

Filter rows:

Showing 1 to 87 of 87 entries

Clinical Trial	Phase	Therapies	Title	Recruitment Status	Covered Countries	Other Countries
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
NCT01089101	Phase Ib/II	Selumetinib	Selumetinib in Treating Young Patients With Recurrent or Refractory Low Grade Glioma	Active, not recruiting		
NCT01659151	Phase II	Aldesleukin Fludarabine Vemurafenib	Vemurafenib With Lymphodepletion Plus Adoptive Cell Transfer and High Dose IL-2 Metastatic Melanoma	Active, not recruiting		
NCT01709292	Phase II	Vemurafenib	Vemurafenib Neoadjuvant Trial in Locally Advanced Thyroid Cancer	Active, not recruiting		
NCT01711632	Phase II	Vemurafenib	BRAF Inhibitor, Vemurafenib, in Patients With Relapsed or Refractory Hairy Cell Leukemia	Active, not recruiting		
NCT01740648	Phase I	Fluorouracil + Trametinib	Trametinib, Fluorouracil, and Radiation Therapy Before Surgery in Treating Patients With Stage II-III Rectal Cancer	Active, not recruiting		
NCT01748149	Phase I	Vemurafenib	Vemurafenib in Children With Recurrent/Refractory BRAF Gene V600E (BRAFFV600E)-Mutant Gliomas	Active, not recruiting		
NCT02034110	Phase II	Dabrafenib + Trametinib	Efficacy and Safety of the Combination Therapy of Dabrafenib and Trametinib in Subjects With BRAF V600E- Mutated Rare Cancers	Active, not recruiting		

The **Variant Associated Clinical Trials** tab displays clinical trials that include the selected gene variant as a variant requirement. NCTID buttons navigate to the 'Clinical Trial Detail Page'. Recruitment status updates daily.

# Explore By Gene Variant

Variant Level Evidence 323   Complex Molecular Profile Evidence 186   Extended Evidence 128   Gene Level Evidence 1031   Treatment Approach Evidence 145   Variant Associated Clinical Trials 87

Gene Associated Clinical Trials 309

## Gene Associated Clinical Trials

Filtering and Sorting ⓘ

Filter rows:

Showing 1 to 309 of 309 entries

Clinical Trial	Phase	Therapies	Title	Recruitment Status	Covered Countries	Other Countries
<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>	<input type="text"/>
NCT01089101	Phase Ib/II	Selumetinib	Selumetinib in Treating Young Patients With Recurrent or Refractory Low Grade Glioma	Active, not recruiting		
NCT01306045	Phase II	Erlotinib   Lapatinib   MK2206   Sunitinib Selumetinib	Molecular Profiling and Targeted Therapy for Advanced Non-Small Cell Lung Cancer, Small Cell Lung Cancer, and Thymic Malignancies	Active, not recruiting		
NCT01436656	Phase I	Encorafenib	A Phase I Study of Oral LGX818 in Adult Patients With Advanced or Metastatic BRAF Mutant Melanoma	Active, not recruiting		
NCT01543698	Phase Ib/II	Binimetinib + Encorafenib Binimetinib + Encorafenib + Ribociclib	A Phase Ib/II Study of LGX818 in Combination With MEK162 in Adult Patients With BRAF Dependent Advanced Solid Tumors	Active, not recruiting		
NCT01657591	Phase I	Vemurafenib + XL888	Study of XL888 With Vemurafenib for Patients With Unresectable BRAF Mutated Stage III/IV Melanoma	Active, not recruiting		
NCT01659151	Phase II	Aldesleukin   Fludarabine   Vemurafenib	Vemurafenib With Lymphodepletion Plus Adoptive Cell Transfer and High Dose IL-2 Metastatic Melanoma	Active, not recruiting		

The **Gene Associated Clinical Trials** tab displays clinical trials that include any gene variant specific to the gene for the selected gene variant.