



CANCER GENOMICS CONSORTIUM

Educating for Best Practices in Clinical Cancer Genomics




CIViC – Clinical Interpretations of Variants in Cancer

www.civicdb.org

<http://www.nature.com/ng/journal/v49/n2/full/ng.3774.html>

CIViC Homepage



The screenshot shows the CIViC homepage with a dark purple background. At the top left is the CIViC logo with the tagline 'CLINICAL INTERPRETATIONS OF VARIANTS IN CANCER'. To the right are navigation links: About, Participate, Community, Help, FAQ, and Sign In/Sign Up. Below these is a search bar labeled 'Go to Genes & Variants' with a 'Go!' button. Underneath the search bar are three buttons: BROWSE, SEARCH, and ACTIVITY. The main content area is divided into several sections. On the left, there's a circular icon with a magnifying glass and the text 'Discover supported clinical interpretations of mutations related to cancer.' To the right, there's a circular icon with several magnifying glasses and the text 'Participate with colleagues to add variants and support for cancer-related mutations.' Below these are two text boxes. The first, 'The Precision Medicine Revolution', describes precision medicine and its application in cancer. The second, 'CIViC's Role in Precision Medicine', states the goal of centralizing and interpreting clinical information. Below these are two columns of statistics. The left column, 'Database and Community Statistics', shows counts for Genes, Variants, Evidence Items, Drugs, Diseases, Publications, Revisions, Contributors, and Comments. The right column, 'CIViC Activity', shows recent user activity, including revisions and comments. At the bottom left is the Cancer Genomics Consortium logo.

CIViC
CLINICAL INTERPRETATIONS OF
VARIANTS IN CANCER

About Participate Community Help FAQ Sign In/Sign Up

Go to Genes & Variants Go!

BROWSE SEARCH ACTIVITY

Discover supported clinical interpretations of mutations related to cancer.

Participate with colleagues to add variants and support for cancer-related mutations.

The Precision Medicine Revolution

Precision medicine refers to the use of prevention and treatment strategies that are tailored to the unique features of each individual and their disease. In the context of cancer this might involve the identification of specific mutations shown to predict response to a targeted therapy. The biomedical literature describing these associations is large and growing rapidly. Currently these interpretations exist largely in private or encumbered databases resulting in extensive repetition of effort.

CIViC's Role in Precision Medicine

Realizing precision medicine will require this information to be centralized, debated and interpreted for application in the clinic. **CIViC is an open access, open source, community-driven web resource for Clinical Interpretation of Variants in Cancer.** Our goal is to enable precision medicine by providing an educational forum for dissemination of knowledge and active discussion of the clinical significance of cancer genome alterations.

Database and Community Statistics

Genes	Variants	Evidence Items
This Week: 1	This Week: 2	This Week: 6
This Month: 4	This Month: 13	This Month: 30
This Year: 98	This Year: 330	This Year: 798
Total: 289	Total: 744	Total: 1737

Drugs	Diseases	Publications
This Week: 4	This Week: 0	This Week: 4
This Month: 10	This Month: 0	This Month: 16
This Year: 117	This Year: 60	This Year: 472
Total: 305	Total: 171	Total: 1106

Revisions	Contributors	Comments
This Week: 82	This Week: 11	This Week: 183

CIViC Activity

- MalachiGriffith** 36 minutes ago
accepted a revision to variant MLH1 / G65D
- MalachiGriffith** 37 minutes ago
accepted a revision to variant MLH1 / G65D
- MalachiGriffith** 37 minutes ago
commented on a suggested revision to MLH1 / G65D
- MalachiGriffith** about an hour ago
accepted a revision to evidence item MLH1 / G65D / EID1823
- MalachiGriffith** about an hour ago
commented on a suggested revision to MLH1 / G65D / EID1823

Aim Statement

Recent Activity

Curation
Stats

Links at Bottom of Homepage

[Glossary of Terms](#) [API Documentation](#) [Data Releases](#) [Presentation Graphics](#) [Meetings and Events](#) [Statistics](#) [Contact](#)

- Glossary of Terms:
 - Evidence levels – A, B, C, D, E
 - Evidence types – Diagnostic, Predictive, Predisposing, Prognostic
 - Evidence/trust ratings – 1 – 5 stars
 - Various therapeutic terms
 - Commonly used terms
 - Abbreviations

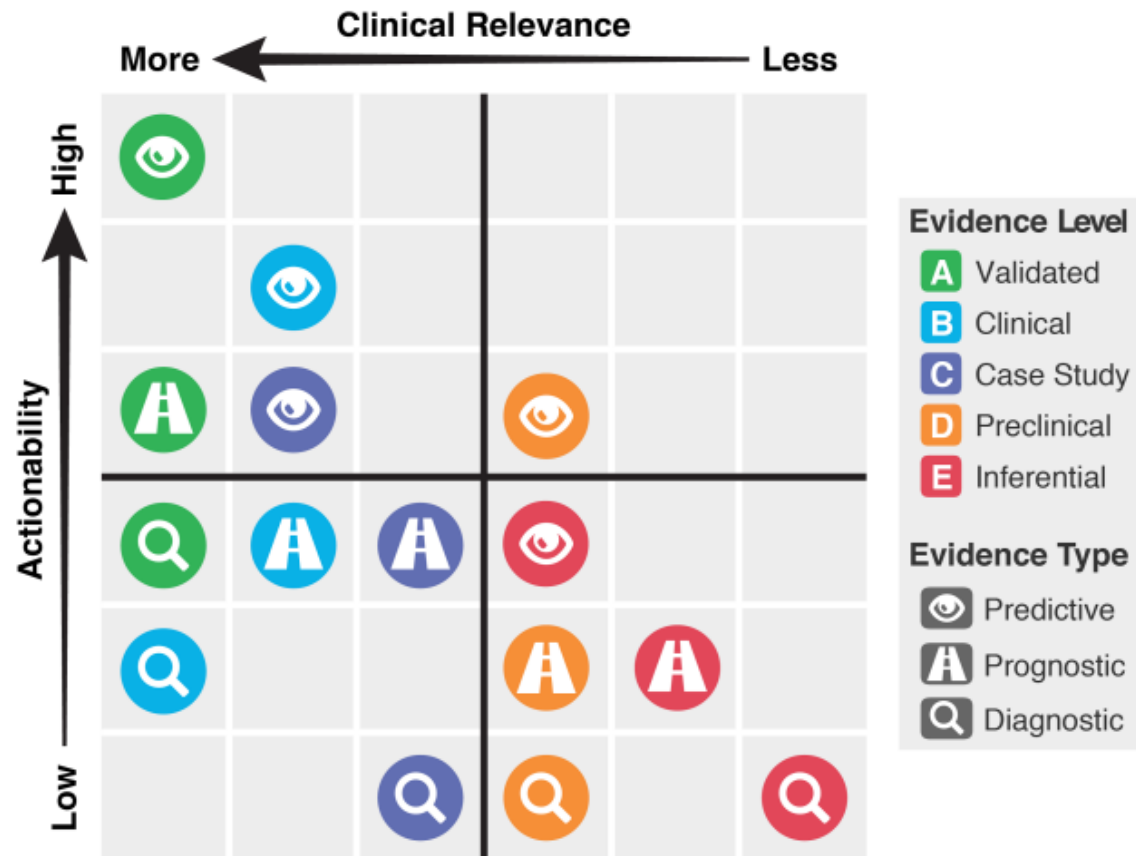
Evidence Level Definitions

Level	Definition	Examples and further comments
A Validated association	Proven/consensus association in human medicine.	<i>"AML with mutated NPM1" is a provisional entity in WHO classification of acute myeloid leukemia (AML). This mutation should be tested for in clinical trials and is recommended for testing in patients with cytogenetically normal AML.</i> Validated associations are often in routine clinical practice already or are the subject of major clinical trial efforts.
B Clinical evidence	Clinical trial or other primary patient data supports association.	<i>BRAF V600E is correlated with poor prognosis in papillary thyroid cancer in a study of 187 patients with PTC and other thyroid diseases.</i> The evidence should be supported by observations in multiple patients. Additional support from functional data is desirable but not required.
C Case study	Individual case reports from clinical journals.	<i>A single patient with FLT3 over-expression responded to the FLT3 inhibitor sunitinib.</i> The study may have involved a large number of patients, but the statement was supported by only a single patient. In some cases, observations from just a handful of patients (e.g. 2-3) or a single family may also be considered a case study/report.
D Preclinical evidence	In vivo or in vitro models support association.	<i>Experiments showed that AG1296 is effective in triggering apoptosis in cells with the FLT3 internal tandem duplication.</i> The study may have involved some patient data, but support for this statement was limited to in vivo or in vitro models (e.g. mouse studies, cell lines, molecular assays, etc.).
E Inferential association	Indirect evidence.	<i>CD33 and CD123 expression were significantly increased in patients with NPM1 mutation with FLT3-ITD, indicating these patients may respond to combined anti-CD33 and anti-CD123 therapy.</i> The assertion is at least one step removed from a direct association between a variant and clinical relevance.

Trust Ratings

- **1-star:** Evidence likely does not belong in CIViC. Claim is not supported well by experimental evidence. Results are not reproducible, or have very small sample size. No follow-up is done to validate novel claims.
- **2-stars:** Evidence is not well supported by experimental data, and little follow-up data is available. Publication is from a journal with low academic impact. Experiments may lack proper controls, have small sample size, or are not statistically convincing.
- **3-stars:** Evidence is convincing, but not supported by a breadth of experiments. May be smaller scale projects, or novel results without many follow-up experiments. Discrepancies from expected results are explained and not concerning.
- **4-stars:** Strong, well supported evidence. Experiments are well controlled, and results are convincing. Any discrepancies from expected results are well-explained and not concerning.
- **5-stars:** Strong, well supported evidence from a lab or journal with respected academic standing. Experiments are well controlled, and results are clean and reproducible across multiple replicates. Evidence confirmed using separate methods.

Evidence Classification and Downstream Clinical Significance



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- API (application programming interface) endpoints open to public use.
 - meant to operate over multiple programming languages.
 - Increases accessibility over various systems.
 - HTTP
 - Many programming languages
 - Command Line

What other genomic applications interact with CIViC?

- Agilent Cartegenia Workbench
- BioGPS
- cBioPortal
- DoCM
- UCSC Browser
- Solve Bio

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- Data Releases: Nightly updates, data archived monthly.
 - Gene Summaries – i.e. PTEN, IDH1
 - Includes URL to gene page and gene summary in cancer context
 - Variant Summaries – i.e. IDH1 R132H
 - Includes genomic coordinates (GRCh37/hg19)
 - Includes reference/variant bases for SNVs
 - Includes transcript information (ENST format)
 - Variant Group Summaries – i.e. ALK fusions
 - Evidence Summaries – each individual primary publication referenced in CIViC = evidence
 - Includes row in .TSV per publication per variant
 - Includes Citation and PMID
 - Evidence Summary in table format
 - All Gene/Variant/Evidence information, including genomic coordinates, base information for SNVs, and URLs

Links at Bottom of Homepage

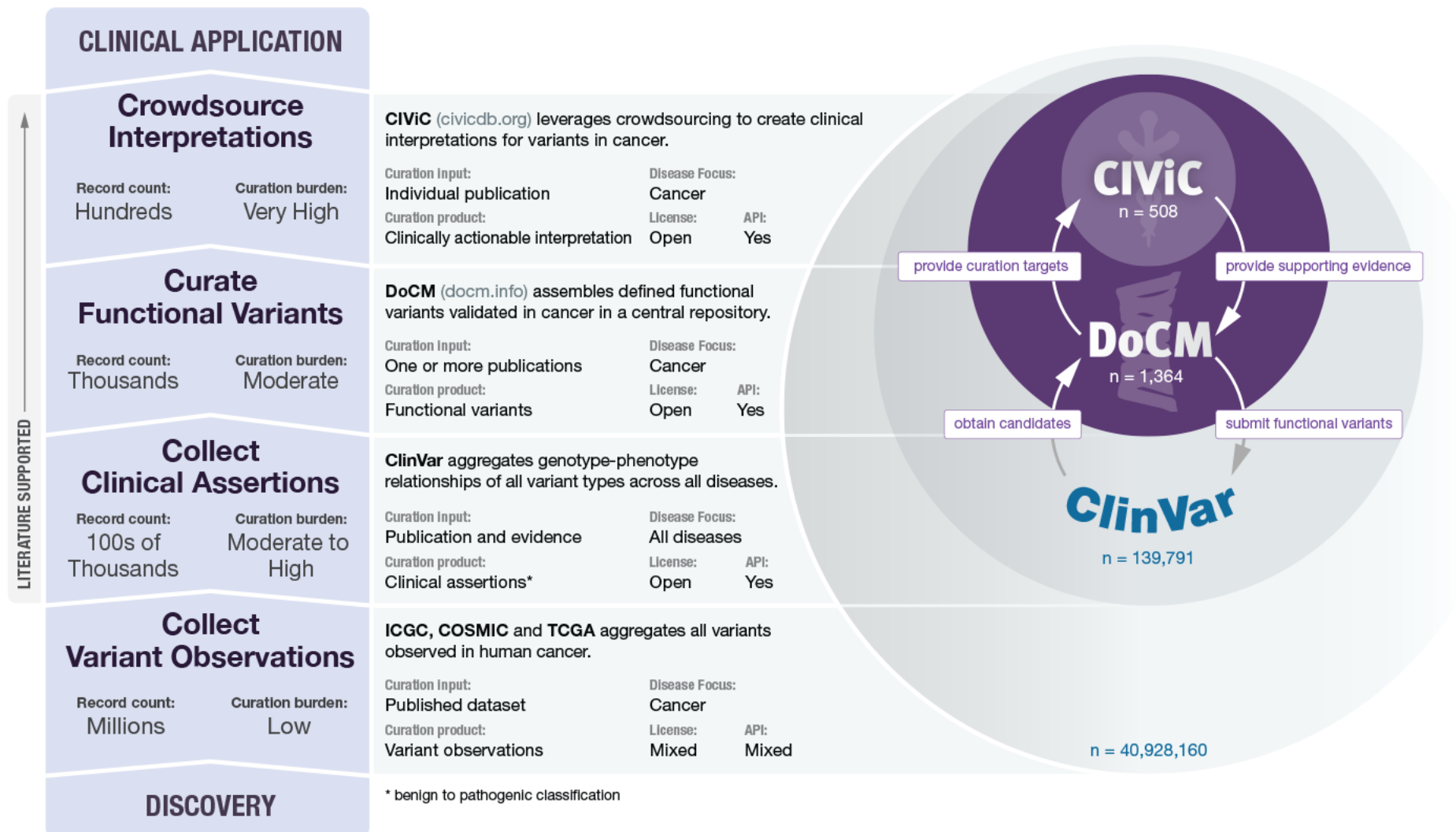
[Glossary of Terms](#) [API Documentation](#) [Data Releases](#) [Presentation Graphics](#) [Meetings and Events](#) [Statistics](#) [Contact](#)

- Meeting and Events
 - Annual Hackathon and Jamboree
 - Open to the crowd-sourcing public
 - Location and date of next Hackathon and Jamboree TBD

Links at Bottom of Homepage

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- Statistics – Pie Charts summarize
 - Evidence – the nature of primary literature used and curation stats
 - Drugs – drugs with information in CIViC.
 - Disease – list of diseases documented in CIViC.
 - Sources Used – Journals that have contributed primary papers to CIViC.
- Contact – lists creators, developers, curators, PI, funding contributors.



Millions of raw sequence reads are produced for a patient tumor.

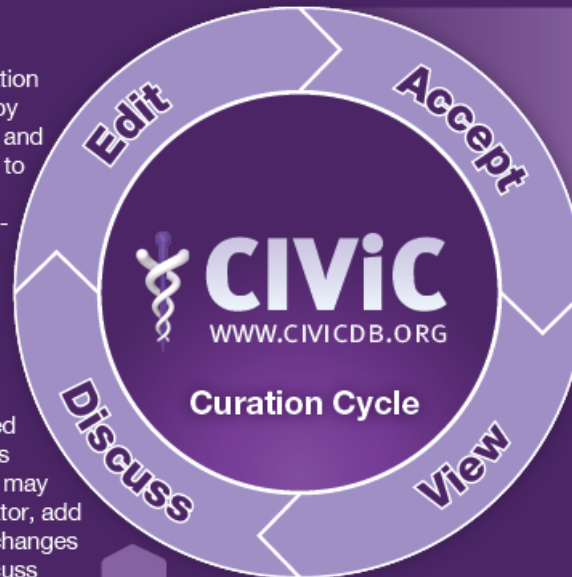


Sequences are aligned to the reference genome and tumor-specific events predicted.



Events are annotated and scored in an effort to predict events of functional significance.

Crowdsourced curation efforts, moderated by experts in oncology and bioinformatics, help to build a knowledge-base of clinical interpretations of variants in cancer, describing the therapeutic, prognostic, diagnostic, and predisposing relevance of inherited and somatic variants of all types. Anyone may sign up to be a curator, add evidence, suggest changes to records, and discuss ongoing curation efforts.



Add New Evidence

[illegible]

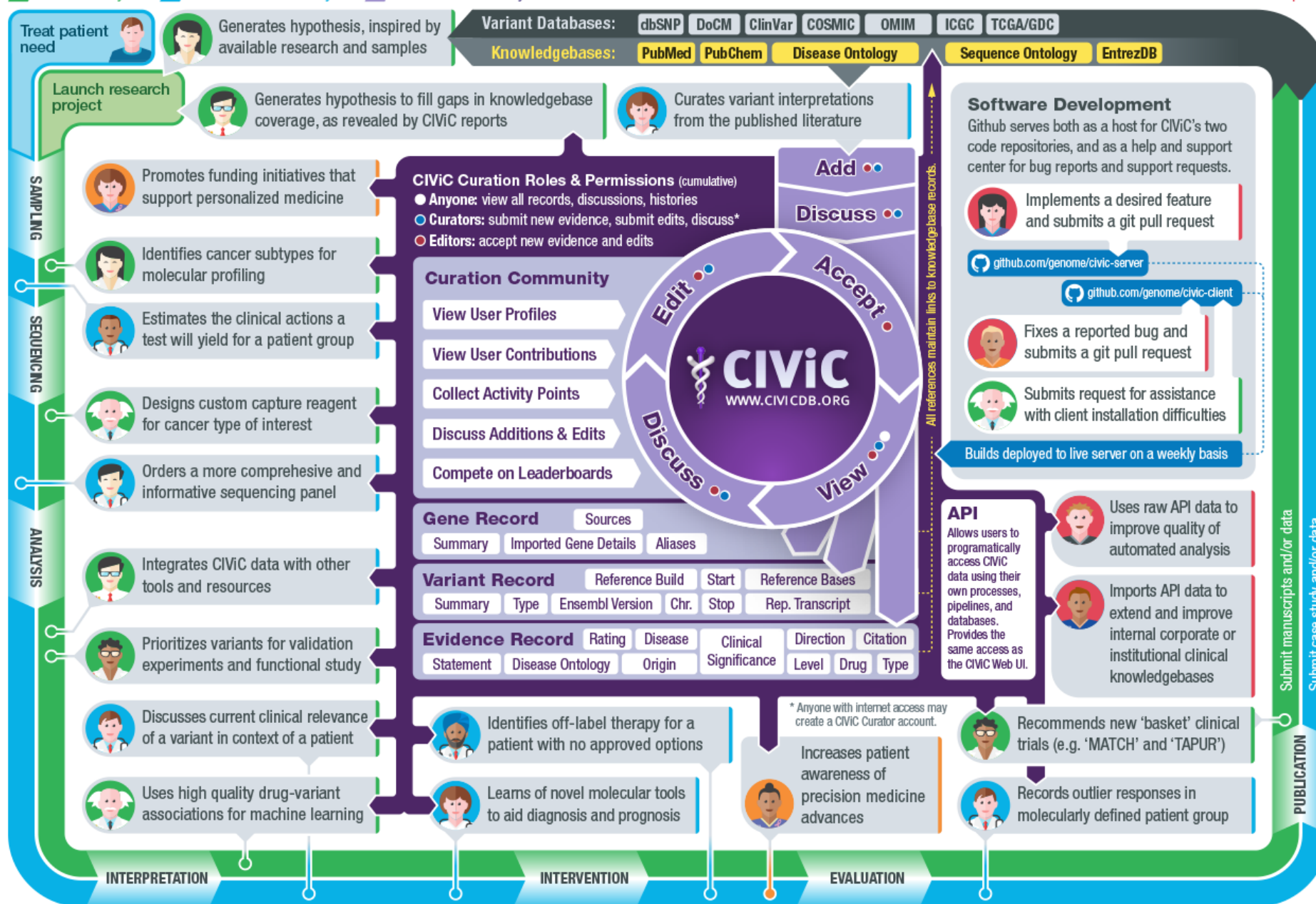
Review and Discuss Edits

[illegible]

Pathologists and oncologists review analysts' reports to help evaluate the significance of potentially clinically actionable events and incorporate into patient care.

▶ Research Cycle
 ▶ Clinical Treatment Cycle
 ▶ CIViC Curation Cycle

● Research Scientist
 ● Clinical Scientist
 ● Patient Advocate
 ● Developer



Using 'Browse' Option

CIViC About Participate Community Help FAQ Sign In/Sign Up

Go to Genes & Variants Go! BROWSE SEARCH ACTIVITY ADD SUGGEST


Browse Variants Genes Variant Groups Sources

Variant	Entrez Gene	Diseases	Drugs	Evidence
AMPLIFICATION	ERBB2	Uterine Corpus Serous Adenocarcinoma, ...	A66, AKT1-1/2, Afatinib, Capecitabine, Cet...	51
V600E	BRAF	Thyroid Cancer, Skin Melanoma, Papillary...	BEZ235 (NVP-BEZ235, Dactolisib), Bevac...	47
EXON 12 MUTATION	NPM1	Acute Myeloid Leukemia	All-trans Retinoic Acid, Anti-CD123, Anti-C...	30
R882	DNMT3A	Acute Myeloid Leukemia	Daunorubicin, Idarubicin,	28
ITD	FLT3	Acute Promyelocytic Leukemia, Acute M...	AG1296, All-trans Retinoic Acid, Anthracy...	27
MUTATION	KRAS	Pseudomyxoma Peritonei, Pancreatic Ad...	AZD5438, AZD8186, Afatinib, BAY 86-976...	25
LOSS	PTEN	Stomach Carcinoma, Stomach Cancer, Pr...	AZD5363, AZD8186, BYL719 (Alpelisib), B...	23
T790M	EGFR	Non-small Cell Lung Carcinoma, Lung Ca...	AEE788, Afatinib, Dacomitinib, Erlotinib, G...	21
ALK FUSIONS	ALK	Non-small Cell Lung Carcinoma, Lung Ad...	Alectinib (CH5424802), CH5424802, Cerit...	21
MUTATION	TP53	Precursor B Lymphoblastic Lymphoma/L...	Alemtuzumab, Chemotherapy, Docetaxel,...	21
MUTATION	PIK3CA	Stomach Cancer, Her2-receptor Positive ...	17-AAG, AZD5363, Anti-EGFR Monoclonal...	18
EXPRESSION	CD274	Stomach Carcinoma, Papillary Thyroid Ca...	Atezolizumab, Avelumab, Ipilimumab, Niv...	14
AMPLIFICATION	FGFR1	Non-small Cell Lung Carcinoma, Lung Sq...	4-hydroxytamoxifen, BGJ-398, BGJ398, D...	14
MUTATION	NRAS	Skin Melanoma, Multiple Myeloma, Mela...	Amuvatinib, Binimetinib (MEK162), Cetux...	13
H1047R	PIK3CA	Thyroid Cancer, Lung Adenocarcinoma, H...	AZD5363, BEZ235 (NVP-BEZ235, Dactolis...	13
V600	BRAF	Non-small Cell Lung Carcinoma, Melanom...	BAY 86-9766, Cetuximab, Dabrafenib, Pa...	12
AMPLIFICATION	MET	Non-small Cell Lung Carcinoma, Lung Sq...	Crizotinib, Erlotinib, Gefitinib, Onartuzum...	12
p16 EXPRESSION	CDKN2A	Oropharynx Cancer, Non-small Cell Lung ...	Afatinib, Cetuximab, EGFR Inhibitor, Panl...	10
MUTATION	BRCA1	Triple-receptor Negative Breast Cancer, O...	Carboplatin, Cediranib, Cisplatin, Olaparib...	10
EXON 19 DELETION	EGFR	Non-small Cell Lung Carcinoma, Lung Ad...	Afatinib, Erlotinib, Gefitinib	10
L858R	EGFR	Non-small Cell Lung Carcinoma, Lung Ad...	Afatinib, Erlotinib, Gefitinib,	10
EXON 2 MUTATION	KRAS	Pancreatic Carcinoma, Pancreatic Cance...	Cetuximab, EGFR Inhibitor, Erlotinib, Gefi...	9
MUTATION	BRCA2	Triple-receptor Negative Breast Cancer, O...	Carboplatin, Cediranib, Cisplatin, Olaparib...	9
EXON 7 MUTATION	WT1	Acute Myeloid Leukemia	Cytarabine, Daunorubicin,	9
G12D	KRAS	Tumor Of Exocrine Pancreas, Pancreatic ...	ARRY-142886, Adoptive T-cell Transfer, B...	9

First Previous 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 ... Next Last

Various Search
Criteria on Variants
and Genes tabs

Variant Groups



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Browse

[Variants](#)
[Genes](#)
[Variant Groups](#)
[Sources](#)

Name	Variants	Count	Genes	Evidence Items ▾
ALK Fusions	RANBP2-ALK, NPM-ALK, EML4-ALK L1196M, EML4-ALK E6...	10	ALK	58
EGFR TKI Resistance	T790M, G12D, G12C, G12A	4	EGFR, KRAS	36
NPM1 Exon 12	W288FS, EXON 12 MUTATION	2	NPM1	35
Other V600's	V600K, V600E+V600M, V600D, V600, L597R	5	BRAF	19
Imatinib Resistance	I843DEL, D1842-843VM, D842Y, D842V, D842I, BCR-ABL T3...	8	ABL1, PDGFRA	18
Crizotinib Resistance	F1174L, EML4-ALK S1206Y, EML4-ALK L1196M, EML4-ALK...	4	ALK	18
KIT Exon 11	V654A, L576P, INTERNAL DUPLICATION, EXON 11 MUTAT...	4	KIT	15
BRAF Fusions	ZKSCAN1-BRAF, TRIM24-BRAF, PPFIBP2-BRAF, PAPSS1-B...	8	BRAF	12
SYT-SSX fusions	SS18-SSX4, SS18-SSX2, SS18-SSX1	3	SSX1, SSX2, SSX4	12
ESR1 Ligand-Binding Domain	Y537S, Y537N, Y537C, L536Q, D538G	5	ESR1	10
HER2 Activating	V842I, V777L, R896C, P780INS, G309A, D769Y, D769H	7	ERBB2	10
BRCA Germline Variants	LOSS-OF-FUNCTION	1	BRCA1, BRCA2	9
Motesanib Resistance	M918T, C634W	2	RET	6
PML-RARa B2 Domain	PML-RARA L218P, PML-RARA A216V, B2 DOMAIN MUTAT...	3	PML	3
FGFR fusions	FGFR3-BAIAP2L1, FGFR2-TACC3, FGFR2-MGEA5	3	FGFR2, FGFR3	3
Kinase Dead BRAF Mutation	K483M, D594V, D594A	3	BRAF	3
TSC Loss	LOSS-OF-FUNCTION, FRAMESHIFT TRUNCATION	2	TSC1	3
KIT Exon 17	D816V	1	KIT	3
PTEN Loss-of-Function	R233*	1	PTEN	2
HEAT domain mutation	K700E, K666N	2	SF3B1	2

Gene Page

Site navigation (points to CIViC logo and navigation bar)

Edit content (points to GENE FLT3 button)

Gene-level interpretation (points to FLT3 gene description and variant information)

Gene variant navigation (points to FLT3 variant list)

Sequence ontology (points to MUTATION, OVEREXPRESSION, T227M, T3D MUTATION, Add Variant Group)

Evidence records (points to Evidence table)

User activity/attribution (points to Submitted by, Accepted by)

Evidence record details (points to Evidence Level, Evidence Type, Evidence Direction, Clinical Significance, Variant Origin)

Disclaimer (points to Disclaimer text)

Sign In/notifications (points to Sign In button)

"Talk page" (comments) (points to Gene Talk button)

Imported gene information (points to Gene Summary box)

Variant-level interpretation (points to Variant Summary box)

Variant coordinates (points to Variant coordinates box)

Data download/table legend (points to Download Data button)

Suggested revision notice (points to Suggested revision notice box)

Disease ontology (points to Disease: Acute Myeloid Leukemia)

Primary literature source (points to Citation: Port et al., 2014, Ann. Hematol.)

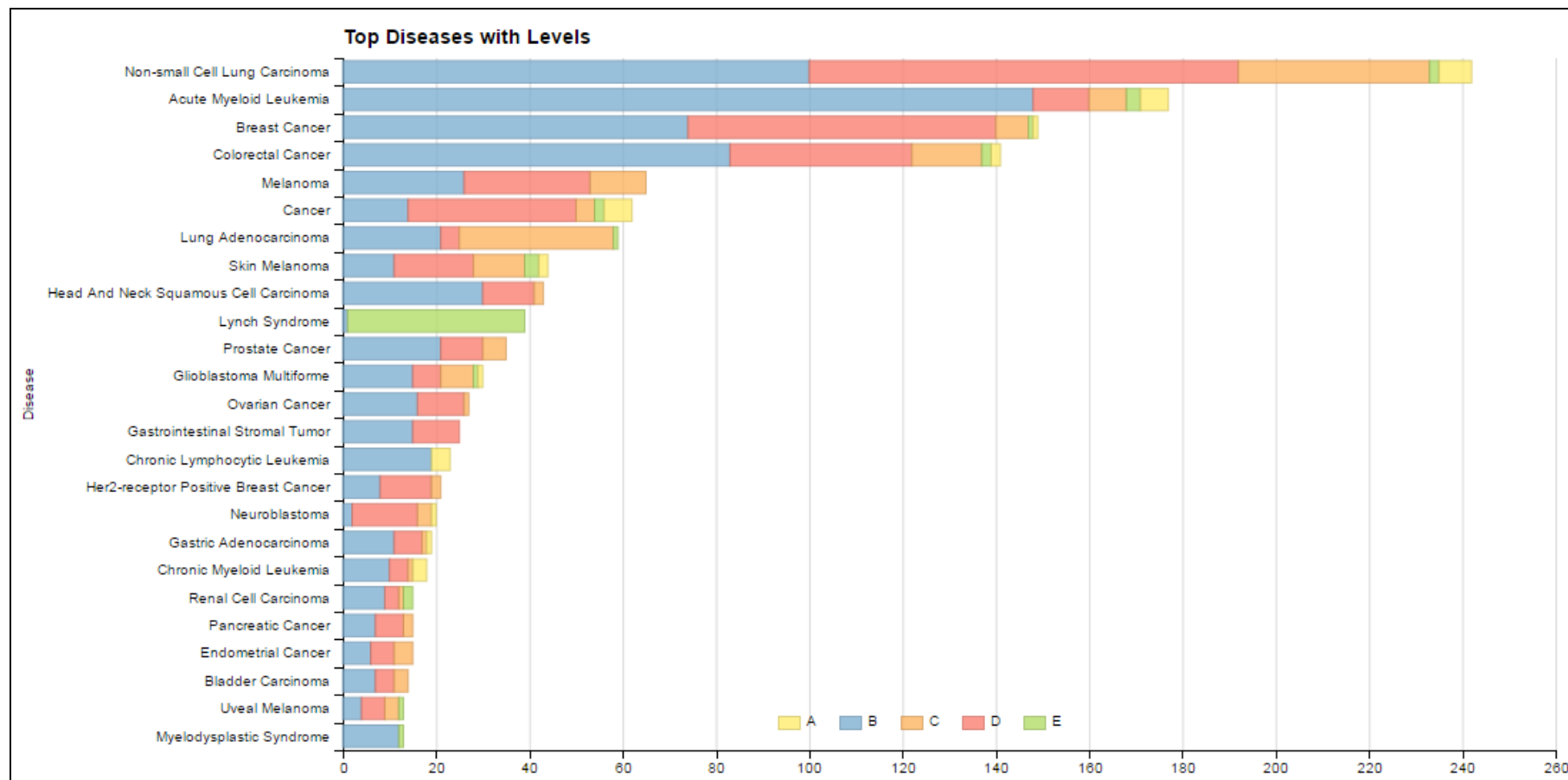
Extensive documentation (points to Glossary of Terms, API Documentation, Data Releases, Presentation Slides, Contact)

CC attribute license (points to CC BY-NC-SA license)

Scenario #1

- You are a laboratory professional designing new disease specific clinical NGS panels.
 - What genes do you include in your Acute Myeloid Leukemia panel?
 - What diseases are best supported by CIViC?

What Disease are best supported by CIViC?



* Click on “Statistics” link at bottom of home page to see this bar graph and other data.

Scenario #1

- You are a laboratory professional designing new disease specific clinical NGS panels.
 - What genes do you include in your Acute Myeloid Leukemia panel?
 - What diseases are best supported by CIViC?

Find Genes and Variants Associated with Disease of Interest: Option #1 "Search"

Go to Genes & Variants

Search Evidence

Example Searches:

Match the following condition:

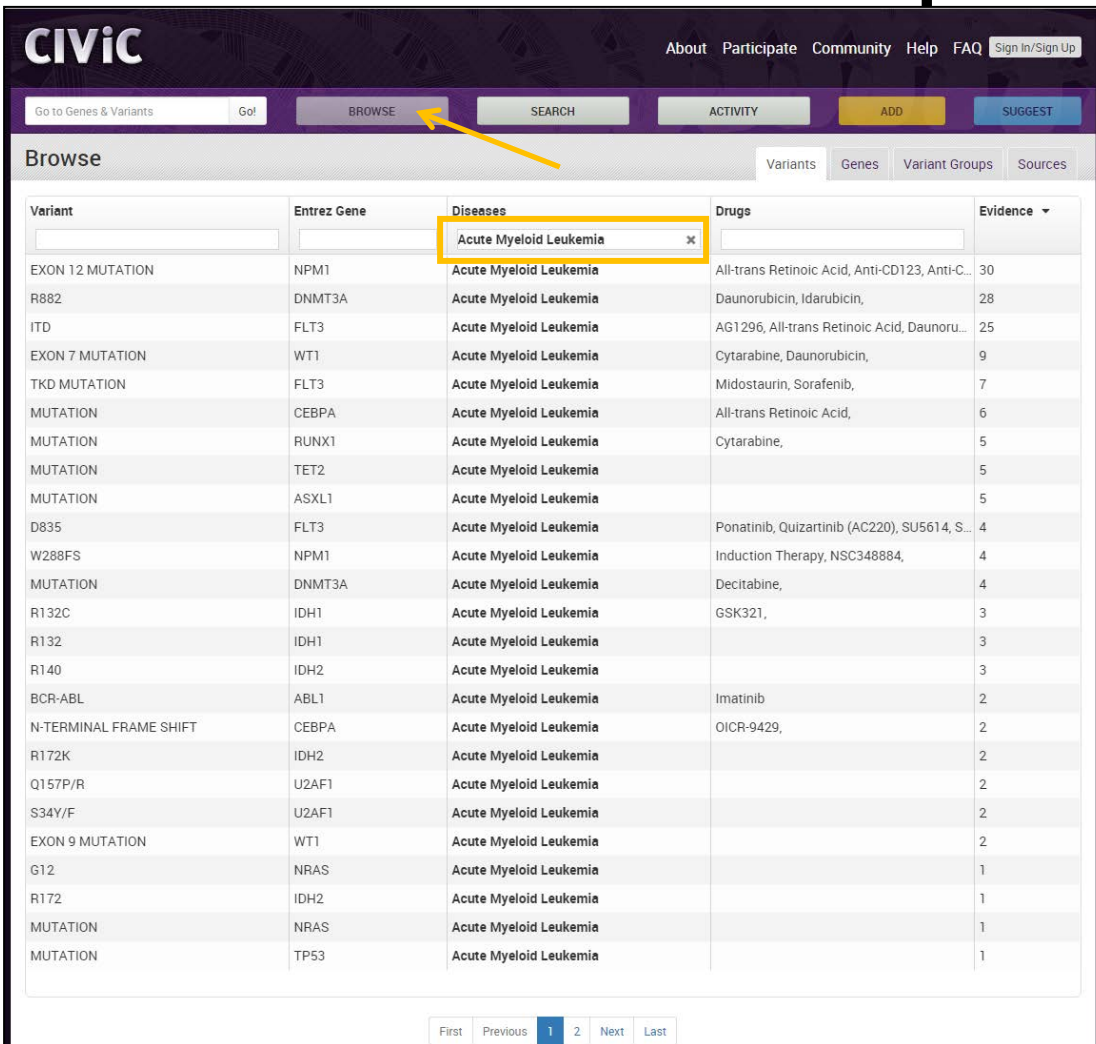
- Using "Search" match the disease name to your disease of interest under the 'Evidence' tab
- Can export data from table as .CSV
- Select any gene/variant from the list to view in more detail.

Search Results 177 total items

EID	GENE	VARIANT	DESC	DIS	DRUGS	EL	ET	ED	CS	VO	TR
116	NPM1	EXON 12 M...	AML with mutated NP...	Acute Myeloid Leukem...	N/A	A	Q	i	Q	...	5 ★
1510	NPM1	W288FS	In a study of 1,540 pat...	Acute Myeloid Leukem...	N/A	A	Q	i	Q	...	5 ★
259	ABL1	BCR-ABL	Treatment of Philadel...	Acute Myeloid Leukem...	Imatinib	A	Q	i	Q	...	5 ★
1029	KMT2A	MLL-MLLT3	The MLL-MLLT3 trans...	Acute Myeloid Leukem...	N/A	A	Q	i	Q	...	4 ★
61	DNMT3...	R882	In a large cohort of yo...	Acute Myeloid Leukem...	N/A	A	A	i	Q	...	3 ★
190	FLT3	ITD	Meta-analysis of studi...	Acute Myeloid Leukem...	N/A	A	A	i	Q	...	3 ★
62	DNMT3...	R882	AML patients with DN...	Acute Myeloid Leukem...	N/A	B	A	i	Q	...	5 ★
64	DNMT3...	R882	In AML patients with F...	Acute Myeloid Leukem...	N/A	B	A	i	Q	...	5 ★
65	DNMT3...	R882	In cytogenetically nor...	Acute Myeloid Leukem...	N/A	B	A	i	Q	...	5 ★
69	FLT3	ITD	In AML patients with F...	Acute Myeloid Leukem...	N/A	B	A	i	Q	...	5 ★
112	DNMT3...	R882	DNMT3A mutations (5...	Acute Myeloid Leukem...	N/A	B	Q	i	Q	...	5 ★
176	NPM1	EXON 12 M...	Complete remission r...	Acute Myeloid Leukem...	N/A	B	A	i	Q	...	5 ★
1514	SRSF2	MUTATION	Patients with Acute M...	Acute Myeloid Leukem...	N/A	B	A	i	Q	...	5 ★
1513	ASXL1	MUTATION	Patients with Acute M...	Acute Myeloid Leukem...	N/A	B	A	i	Q	...	5 ★

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Find Genes and Variants Associated with Disease of Interest: Option #1 “Browse”



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Go to Genes & Variants Go! **BROWSE** SEARCH ACTIVITY ADD SUGGEST

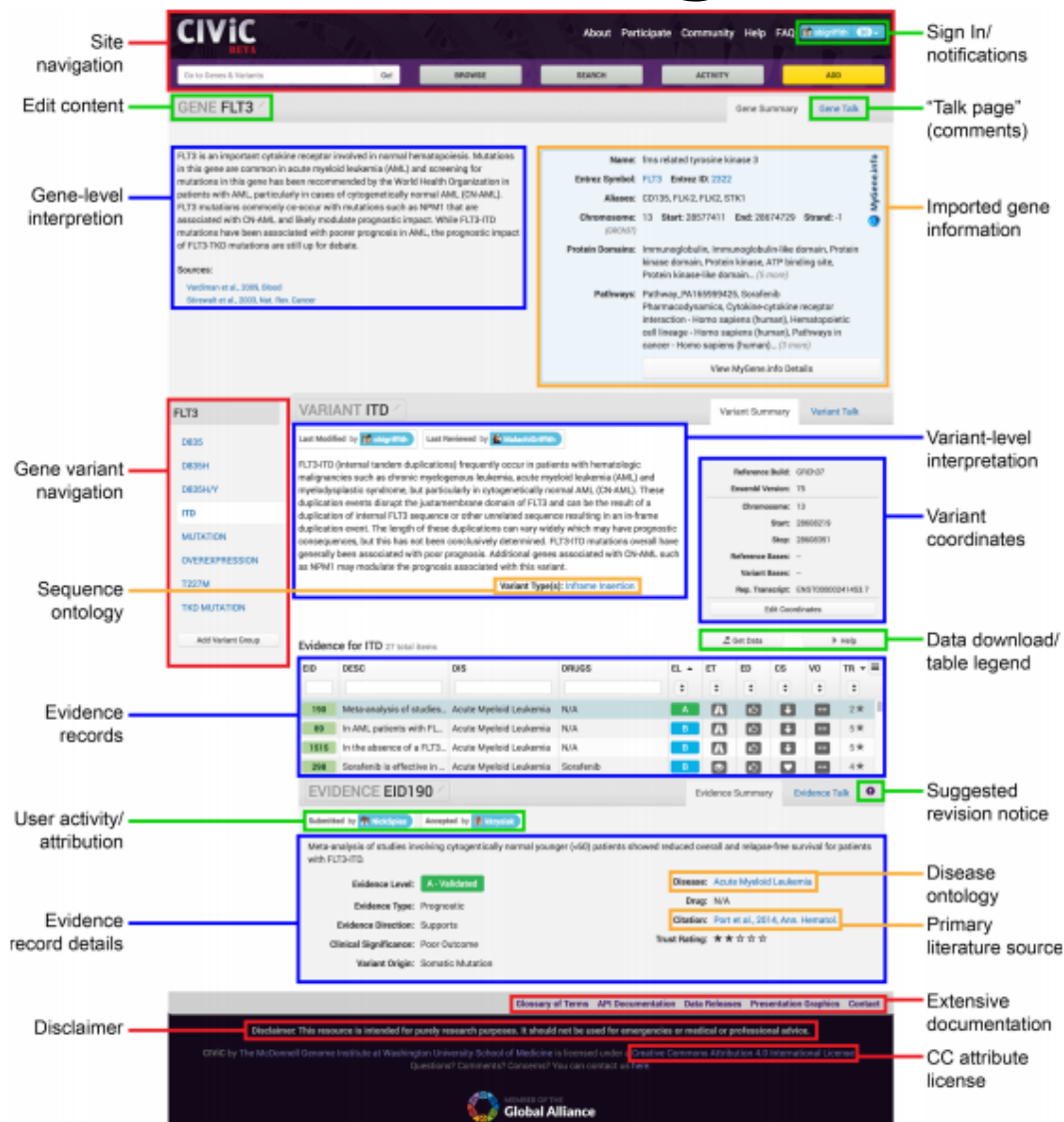
Browse Variants Genes Variant Groups Sources

Variant	Entrez Gene	Diseases	Drugs	Evidence
EXON 12 MUTATION	NPM1	Acute Myeloid Leukemia	All-trans Retinoic Acid, Anti-CD123, Anti-C...	30
R882	DNMT3A	Acute Myeloid Leukemia	Daunorubicin, Idarubicin,	28
ITD	FLT3	Acute Myeloid Leukemia	AG1296, All-trans Retinoic Acid, Daunoru...	25
EXON 7 MUTATION	WT1	Acute Myeloid Leukemia	Cytarabine, Daunorubicin,	9
TKD MUTATION	FLT3	Acute Myeloid Leukemia	Midostaurin, Sorafenib,	7
MUTATION	CEBPA	Acute Myeloid Leukemia	All-trans Retinoic Acid,	6
MUTATION	RUNX1	Acute Myeloid Leukemia	Cytarabine,	5
MUTATION	TET2	Acute Myeloid Leukemia		5
MUTATION	ASXL1	Acute Myeloid Leukemia		5
D835	FLT3	Acute Myeloid Leukemia	Ponatinib, Quizartinib (AC220), SU5614, S...	4
W288FS	NPM1	Acute Myeloid Leukemia	Induction Therapy, NSC348884,	4
MUTATION	DNMT3A	Acute Myeloid Leukemia	Decitabine,	4
R132C	IDH1	Acute Myeloid Leukemia	GSK321,	3
R132	IDH1	Acute Myeloid Leukemia		3
R140	IDH2	Acute Myeloid Leukemia		3
BCR-ABL	ABL1	Acute Myeloid Leukemia	Imatinib	2
N-TERMINAL FRAME SHIFT	CEBPA	Acute Myeloid Leukemia	OICR-9429,	2
R172K	IDH2	Acute Myeloid Leukemia		2
Q157P/R	U2AF1	Acute Myeloid Leukemia		2
S34Y/F	U2AF1	Acute Myeloid Leukemia		2
EXON 9 MUTATION	WT1	Acute Myeloid Leukemia		2
G12	NRAS	Acute Myeloid Leukemia		1
R172	IDH2	Acute Myeloid Leukemia		1
MUTATION	NRAS	Acute Myeloid Leukemia		1
MUTATION	TP53	Acute Myeloid Leukemia		1

First Previous **1** 2 Next Last

- Using “Browse”, type in your disease of interest into the designated box in the variants tab or the genes tab.
- If you search under the genes tab, you won’t have genes duplicated on the list but you lose variant information.
- Not able to export list as .CSV
- Select any gene/variant from the list to view in more detail.

Gene Page



Site navigation: CIVIC logo, About, Participate, Community, Help, FAQ, Sign In/notifications

Edit content: GENE FLT3, Gene Summary, Gene Talk ("Talk page" (comments))

Gene-level interpretation: FLT3 is an important cytokine receptor involved in normal hematopoiesis. Mutations in this gene are common in acute myeloid leukemia (AML) and according to mutations in this gene has been recommended by the World Health Organization in patients with AML, particularly in cases of cytogenetically normal AML (CN-AML). FLT3 mutations commonly co-occur with mutations such as NPM1 that are associated with CN-AML, and likely modulate prognostic impact. While FLT3-ITD mutations have been associated with poorer prognosis in AML, the prognostic impact of FLT3-TKD mutations are still up for debate.

Imported gene information: Name: Fms related tyrosine kinase 3, Entrez Symbol: FLT3, Entrez ID: 2322, Aliases: CD135, FLK2, FLK2, STK1, Chromosome: 13, Start: 2857411, End: 28674729, Strand: -1, Protein Domains: Immunoglobulin, Immunoglobulin-like domain, Protein kinase domain, Protein kinase, ATP binding site, Protein kinase-like domain... (5 more), Pathways: Pathway, PA16599425, Sorafenib Pharmacodynamics, Cytokine-cytokine receptor interaction - Homo sapiens (human), Hematopoietic cell lineage - Homo sapiens (human), Pathways in cancer - Homo sapiens (human)... (3 more), View MyGene Info Details

Gene variant navigation: FLT3, D635, D639H, D635A/Y, ITD, MUTATION, OVEREXPRESSION, T227M, TKD MUTATION, Add Variant Group

Sequence ontology: VARIANT ITD, Variant Summary, Variant Talk

Variant-level interpretation: Last Modified by [user], Last Reviewed by [user], FLT3-ITD (internal tandem duplications) frequently occur in patients with hematologic malignancies such as chronic myelogenous leukemia, acute myeloid leukemia (AML) and myelodysplastic syndrome, but particularly in cytogenetically normal AML (CN-AML). These duplication events disrupt the juxta-membrane domain of FLT3 and can be the result of a duplication of internal FLT3 sequence or other unrelated sequence resulting in an in-frame duplication event. The length of these duplications can vary widely which may have prognostic consequences, but this has not been conclusively determined. FLT3-ITD mutations overall have generally been associated with poor prognosis. Additional genes associated with CN-AML, such as NPM1 may modulate the prognosis associated with this variant. Variant Type(s): in-frame insertion

Variant coordinates: Reference Build: GRCh37, Ensembl Version: 75, Chromosome: 13, Start: 28606219, Stop: 28606391, Reference Base: -, Variant Base: -, Ref. Transcript: ENS0000041453.7, Ref. Coordinates

Data download/table legend: Download Data, Help

Evidence records: Evidence for ITD 27 total items

ID	DISC	DIS	DRUGS	EL	ET	ED	CS	VO	TR	IR
198	Meta-analysis of studies...	Acute Myeloid Leukemia	N/A	6	A	C	3	2	5	2
89	In AML patients with FLT3...	Acute Myeloid Leukemia	N/A	6	A	C	3	2	5	5
181E	In the absence of a FLT3...	Acute Myeloid Leukemia	N/A	6	A	C	3	2	5	5
204	Sorafenib is effective in...	Acute Myeloid Leukemia	Sorafenib	3	C	C	3	2	4	4

Evidence EID190: Submitted to [user], Accepted to [user]

User activity/attribution: Meta-analysis of studies involving cytogenetically normal younger (<60) patients showed reduced overall and relapse-free survival for patients with FLT3-ITD.


Evidence record details: Evidence Level: A: Validated, Evidence Type: Prognostic, Evidence Direction: Supports, Clinical Significance: Poor Outcome, Variant Origin: Somatic Mutation, Disease: Acute Myeloid Leukemia, Drug: N/A, Citation: Port et al, 2014, Ann. Hematol., Trust Rating: ★★☆☆☆

Disclaimer: Disclaimer: This resource is intended for purely research purposes. It should not be used for emergencies in medical or professional offices. CIVIC by The McDonnell Genome Institute at Washington University School of Medicine is licensed under Creative Commons Attribution 4.0 International License. Question? Comment? Concern? You can contact us here.

Extensive documentation: Glossary of Terms, API Documentation, Data Releases, Presentation Graphics, Contact

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Reference back to PMID/other CIViC entries from same citation



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Katayama et al., 2012, Sci Transl Med Summary

Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers.

Authors: Ryohel Katayama, Alice T Shaw, Tahsin M Khan, Mari Mino-Kenudson, Benjamin J Solomon, Balazs Halmos, Nicholas A Jessop, John C Wain, Alan Tien Yeo, Cyril Benes, Lisa Drew, Jamal Carlos Saeh, Katherine Crosby, Leticia V Sequist, A John Iafrate, Jeffrey A Engelman

Abstract: Most anaplastic lymphoma kinase (ALK)-positive non-small cell lung cancers (NSCLCs) are highly responsive to treatment with ALK tyrosine kinase inhibitors (TKIs). However, patients with these cancers invariably relapse, typically within 1 year, because of the development of drug resistance. Herein, we report findings from a series of lung cancer patients (n = 18) with acquired resistance to the ALK TKI crizotinib. In about one-fourth of patients, we identified a diverse array of secondary mutations distributed throughout the ALK TK domain, including new resistance mutations located in the solvent-exposed region of the adenosine triphosphate-binding pocket, as well as amplification of the ALK fusion gene. Next-generation ALK inhibitors, developed to overcome crizotinib resistance, had differing potencies against specific resistance mutations. In addition to secondary ALK mutations and ALK gene amplification, we also identified aberrant activation of other kinases including marked amplification of KIT and increased autophosphorylation of epidermal growth factor receptor in drug-resistant tumors from patients. In a subset of patients, we found evidence of multiple resistance mechanisms developing simultaneously. These results highlight the unique features of TKI resistance in ALK-positive NSCLCs and provide the rationale for pursuing combinatorial therapeutics that are tailored to the precise resistance mechanisms identified in patients who relapse on crizotinib treatment.

Published: 2012-2-8

Citation: Katayama et al., 2012, Sci Transl Med

Pubmed ID: [22277784](#)

Journal: Science translational medicine

PMC ID: PMC3385512

Status: fully curated

Evidence Supported by Katayama et al., 2012, Sci Transl Med 10 total items

EID	GENE	VARIANT	DESC	DIS	DRUGS	EL	ET	ED	CS	VO	TR
444	ALK	EML4-ALK...	A lung adenocarcinom...	Non-small Cell Lung C...	Crizotinib	C				...	4 ★
1357	ALK	ALK FUSIO...	A patient with ALK-rea...	Lung Adenocarcinoma	Crizotinib	C				...	3 ★
443	ALK	EML4-ALK...	The S1206Y mutation...	Non-small Cell Lung C...	Crizotinib	D				...	4 ★
442	ALK	EML4-ALK...	The L1196M mutation...	Non-small Cell Lung C...	Crizotinib	D				...	4 ★
441	ALK	ALK FUSIO...	The G1202R mutation...	Non-small Cell Lung C...	Crizotinib	D				...	4 ★
1348	ALK	EML4-ALK...	Treatment of Ba/F3 c...	Non-small Cell Lung C...	TAE684	D				...	3 ★
1347	ALK	EML4-ALK...	Ba/F3 cells expressin...	Non-small Cell Lung C...	Alectinib (CH5424802)	D				...	3 ★

Source Comments
 No Comments for this Source.

- Click on Citation link on bottom of gene/variant page.
- Evidence Summary page has article information and abstract
- List of Evidence items associated with primary publication near bottom of page.

Scenario #2

- You are trying to interpret a complex WES report on an ovarian cancer patient.
 - How do you narrow down pathogenic variants that may be actionable in your patient's report?
 - TP53 – P72R
 - PIK3CA – amplification
 - AKT1 – E17K
 - AKT2 – amplification
 - CBFB – mutation
 - CASP8 – D302H

Search Gene/Variant Pages for Therapeutic Information

PIK3CA Variants

filter variants...

AMPLIFICATION

E542K

E545K

EXON 10 MUTATION

EXON 21 MUTATION

H1047R

MUTATION

P471L

VARIANT AMPLIFICATION

Variant Summary

Variant Talk

Last Modified by LynzeyK

Last Reviewed by bainscou

This Variant does not currently have a Summary.

Variant Type:
Transcript Amplification

HGVS Expression:
None specified.

ClinVar ID:
N/A

Ref. Build: GRCh37 Ensembl Version: 75

Chr.	Start	Stop	Ref. Bases	Var. Bases
3	178866311	178957881	--	--

Rep. Transcript: ENST00000263967.3

Evidence for AMPLIFICATION 4 total items

Get Data

Help

EID	DESC	DIS	DRUGS	EL	ET	ED	CS	VO	TR
504	In patients with gastric cancer...	Gastric Adenocarcinoma	N/A	B	A	👍	↓	...	3 ★
756	One platinum-refractory epithe...	Epithelial Ovarian Cancer	Pictilisib	C	👁	👍	♥	...	2 ★
1403	474 cancer cell lines from the ...	Stomach Carcinoma	BYL719 (Alpelisib)	D	👁	👍	♥	...	3 ★
1464	The HNSCC cell line LB771 wit...	Head And Neck Squamous Ce...	Taselisib (GDC-0032)	D	👁	👍	♥	...	1 ★

Scenario #2 - Results

- You are a laboratory consultant with a complex WES report on an ovarian cancer patient.
 - How do you narrow down pathogenic variants that may be actionable in your patient's report?
 - TP53 – P72R
 - PIK3CA – amplification
 - AKT1 – E17K
 - AKT2 – amplification
 - CBFB – mutation
 - CASP8 – D302H

Scenario #3

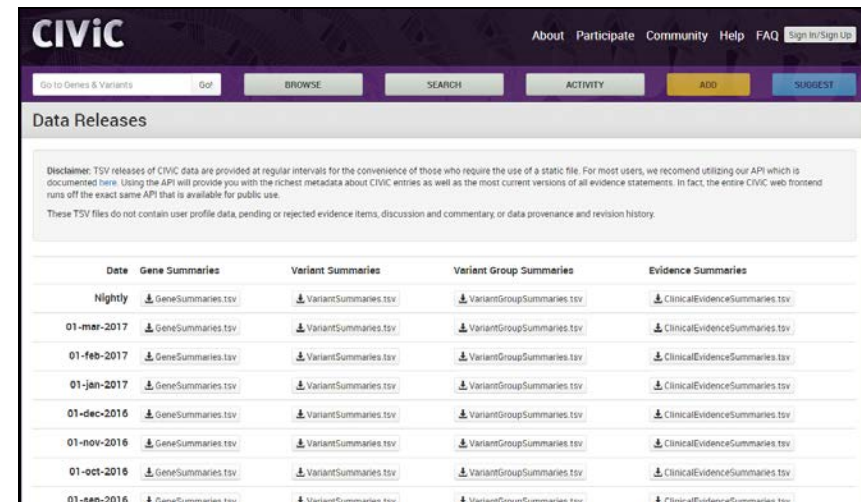
- You have been given the task of putting together a Pan Cancer List for your laboratory/institution.
 - Which genes should be included in your list?

Pan Cancer List

- All variants/genes/rearrangements documented in CIViC are evidence-based.
- Do you want to include all genes from CIViC?
 - If so, document in your own internal database that these entries to your Pan Cancer List are described in CIViC.
 - Include links to CIViC if possible

Download Data Release

- Download desired data release from CIViC
 - Click on Data Release in bottom banner.
 - Select appropriate .TSV file
 - Likely gene and/or variant file.
 - Add to pan cancer list format of choice



The screenshot shows the CIViC website's 'Data Releases' section. It includes a disclaimer about the use of TSV files and a table of available data releases. The table has columns for Date, Gene Summaries, Variant Summaries, Variant Group Summaries, and Evidence Summaries. Each row represents a specific date and provides download links for each of these categories.

Date	Gene Summaries	Variant Summaries	Variant Group Summaries	Evidence Summaries
Nightly	GeneSummaries.tsv	VariantSummaries.tsv	VariantGroupSummaries.tsv	ClinicalEvidenceSummaries.tsv
01-mar-2017	GeneSummaries.tsv	VariantSummaries.tsv	VariantGroupSummaries.tsv	ClinicalEvidenceSummaries.tsv
01-feb-2017	GeneSummaries.tsv	VariantSummaries.tsv	VariantGroupSummaries.tsv	ClinicalEvidenceSummaries.tsv
01-jan-2017	GeneSummaries.tsv	VariantSummaries.tsv	VariantGroupSummaries.tsv	ClinicalEvidenceSummaries.tsv
01-dec-2016	GeneSummaries.tsv	VariantSummaries.tsv	VariantGroupSummaries.tsv	ClinicalEvidenceSummaries.tsv
01-nov-2016	GeneSummaries.tsv	VariantSummaries.tsv	VariantGroupSummaries.tsv	ClinicalEvidenceSummaries.tsv
01-oct-2016	GeneSummaries.tsv	VariantSummaries.tsv	VariantGroupSummaries.tsv	ClinicalEvidenceSummaries.tsv
01-sep-2016	GeneSummaries.tsv	VariantSummaries.tsv	VariantGroupSummaries.tsv	ClinicalEvidenceSummaries.tsv

Scenario #4

- You would like to see all possible high quality evidence pertaining to treatment for colorectal cancer patients with NRAS mutation.
 - Advanced Search
 - Gene Name: NRAS
 - Trust Rating: greater than or equal to 3 stars
 - Evidence Level: above C – Case Study
 - Disease Name: Colorectal Cancer (DOID: 9256)

[Go to Genes & Variants](#)
[Go!](#)
[BROWSE](#)
[SEARCH](#)
[ACTIVITY](#)
[ADD](#)
[SUGGEST](#)

Search Evidence

[Evidence](#)
[Variants](#)
[Genes](#)
[Sources](#)

Example Searches:

[High Quality ALK Evidence](#)
[High Quality Predictive Evidence](#)
[High Quality Drug Predictions](#)
[Alectinib Evidence](#)

Match all of the following conditions:

✕

✕

✕

✕
+

Colorectal Cancer (DOID: 9256)

Colorectal Adenocarcinoma (DOID: 0050861)

[Search](#)

Search Results 3 total items

[Get Data](#)
[Help](#)

EID	GENE	VARIANT	DESC	DIS	DRUGS	EL	ET	ED	CS	VO	TR
27	NRAS	MUTATION	Patients with colorect...	Colorectal Cancer	N/A	B					3 ★
36	NRAS	Q61	Chemotherapy-refract...	Colorectal Cancer	Cetuximab	B					3 ★
124	NRAS	Q61	In chemotherapy-refra...	Colorectal Cancer	Cetuximab	B					3 ★

* Start with an Example Search if your query is similar

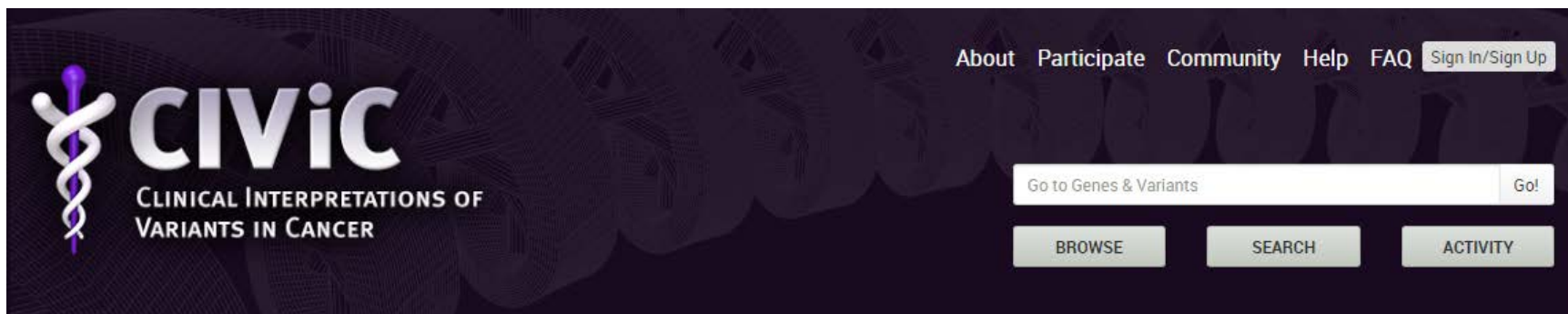
* Enter, add, or remove search criteria to match your query

* Look for evidence items with drugs identified.

Scenario #5

- You are looking into creating a genomic knowledgebase for your institution.
 - How can you create a symbiotic relationship between your knowledgebase and CIViC?
 - Use links to CIViC in your knowledgebase
 - Use CIViC API – find information on bottom banner “API Documentation” (See slide 6)
 - Cite CIViC whenever applicable (See slide 1)
 - Join the CIViC crowd-source curation efforts
 - Join VICC – Variant Interpretation in Cancer Consortium (<http://cancervariants.org/>)

Joining CIViC Community



- Sign up with Google account using button in upper right hand corner.
 - Link account to Twitter, Facebook, LinkedIn
 - Activity will be tracked by CIViC moderators

CIViC Assessment of Knowledgebase Silos

	Cancer Genome Interpreter (CGI)	CanDL (CDL) ¹	Gene Drug Knowledge Database (GDKD) ²	OncoKb (OKB)	Precision Medicine Knowledge base (PMKB)	Jackson Knowledge base (JKB) ³	My Cancer Genome (MCG) ⁴
Total unique publications	530	126	409	3,700	560	787	840
Percentage of publications in this resource found in CIViC	21.9%	24.6%	26.9%	6.8%	6.6%	8.6%	14.9%
Percentage of publications in CIViC found in this resource	13.0%	3.4%	12.3%	1.6%	4.1%	7.6%	14.0%
Total overlapping publications with CIViC	116	30	110	61	37	68	125
Maximum overlapping publications with any other resource	293 (55.3%) (GDKD)	38 (30.2%) (MCG)	293 (71.6%) (CGI)	91 (2.5%) (PMKB)	91 (16.3%) (OKB)	73 (9.3%) (MCG)	125 (14.9%) (CIViC)

CIViC Video Tutorials

- https://www.youtube.com/watch?v=TP_a1za7gJQ
- <https://www.youtube.com/watch?v=-d6mjtzwwrA>

CIViC Contacts

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