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

Aim Statement

Recent Activity

Curation Stats

CANCER GENOMICS CONSORTIUM

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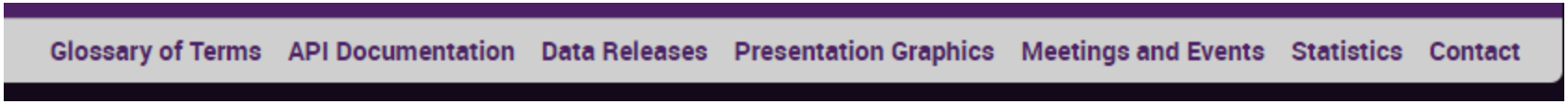
Links at Bottom of Homepage



- 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

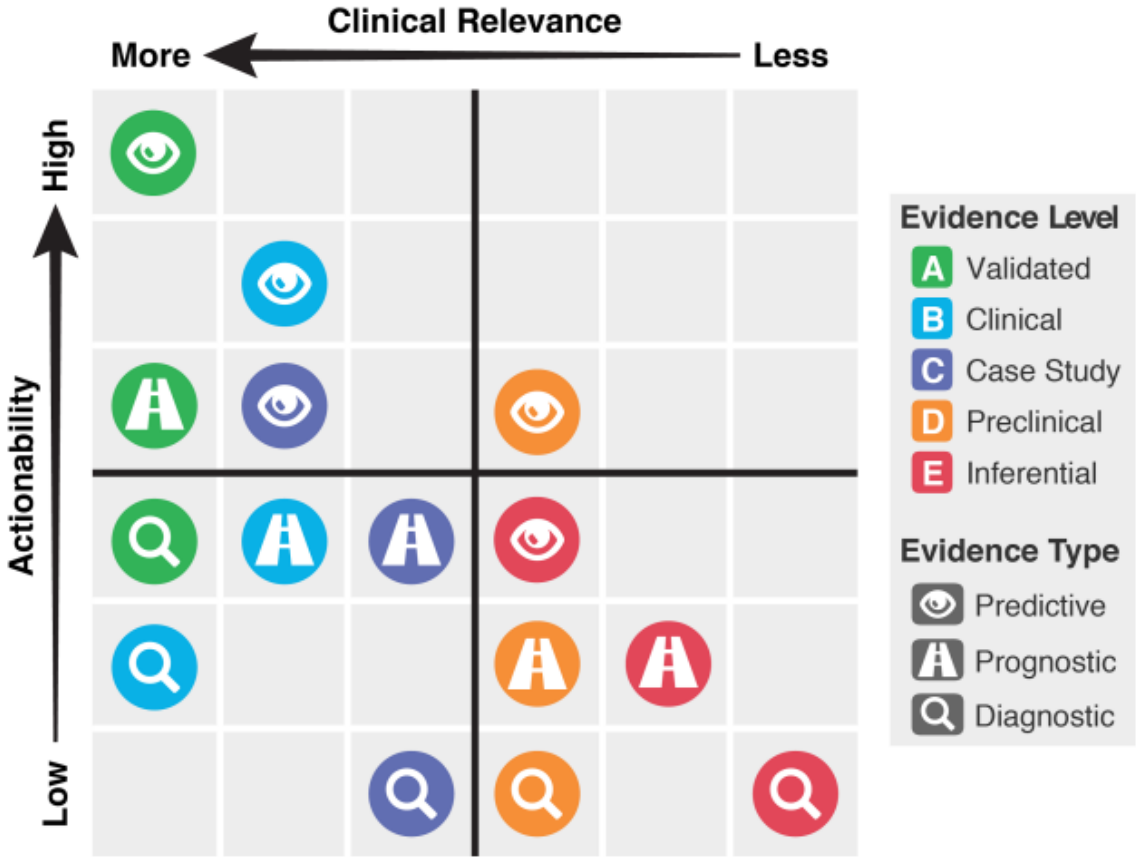
Evidence Level Definitions

Level	Definition	Examples and further comments
A Validated association	Proven/consensus association in human medicine.	*"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 cytogentically normal AML.* 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.	*BRAF V600E is correlated with poor prognosis in papillary thyroid cancer in a study of 187 patients with PTC and other thyroid diseases.* 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.	*A single patient with FLT3 over-expression responded to the FLT3 inhibitor sunitinib.* 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.	*Experiments showed that AG1296 is effective in triggering apoptosis in cells with the FLT3 internal tandem duplication.* 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.	*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.* 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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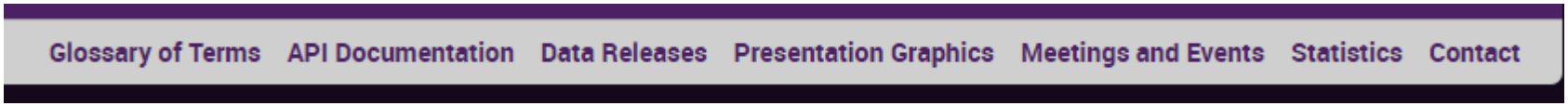

- API (application programming interface) endpoints open to public use.
  - meant to operate over multiple programming languages.
  - Increases accessibility over various systems.
    - HTTP
    - Many programming languages
    - Command Line

What other genomic applications interact with CIViC?

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

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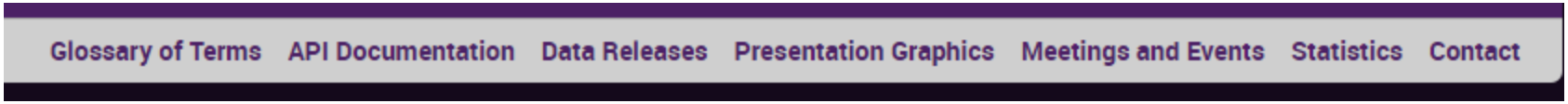

- Data Releases: Nightly updates, data archived monthly.
  - Gene Summaries – i.e. PTEN, IDH1
    - Includes URL to gene page and gene summary in cancer context
  - Variant Summaries – i.e. IDH1 R132H
    - Includes genomic coordinates (GRCh37/hg19)
    - Includes reference/variant bases for SNVs
    - 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

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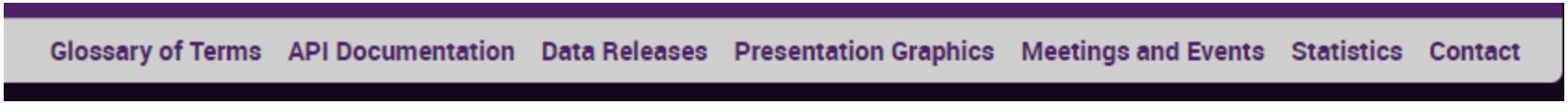

- Meeting and Events
  - Annual Hackathon and Jamboree
    - Open to the crowd-sourcing public
    - Location and date of next Hackathon and Jamboree TBD

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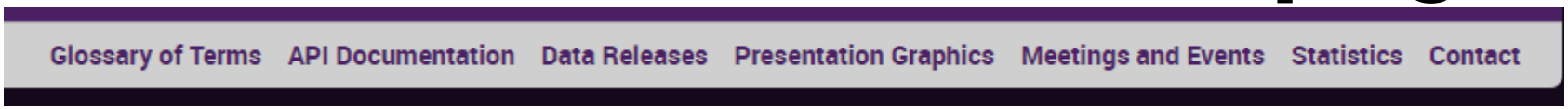


- Statistics – Pie Charts summarize
  - Evidence – the nature of primary literature used and curation stats
  - Drugs – drugs with information in CIViC.
  - Disease – list of diseases documented in CIViC.
  - Sources Used – Journals that have contributed primary papers to CIViC.
- Contact – lists creators,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

CIViC

CLINICAL APPLICATION

LITERATURE SUPPORTED

Crowdsource Interpretations

Record count: Hundreds
Curation burden: Very High

CIViC (civicdb.org) leverages crowdsourcing to create clinical interpretations for variants in cancer.

Curation Input: Individual publication
Disease Focus: Cancer
Curation product: Clinically actionable interpretation
License: Open
API: Yes

Curate Functional Variants

Record count: Thousands
Curation burden: Moderate

DoCM (docm.info) assembles defined functional variants validated in cancer in a central repository.

Curation Input: One or more publications
Disease Focus: Cancer
Curation product: Functional variants
License: Open
API: Yes

Collect Clinical Assertions

Record count: 100s of Thousands
Curation burden: Moderate to High

ClinVar aggregates genotype-phenotype relationships of all variant types across all diseases.

Curation Input: Publication and evidence
Disease Focus: All diseases
Curation product: Clinical assertions*
License: Open
API: Yes

Collect Variant Observations

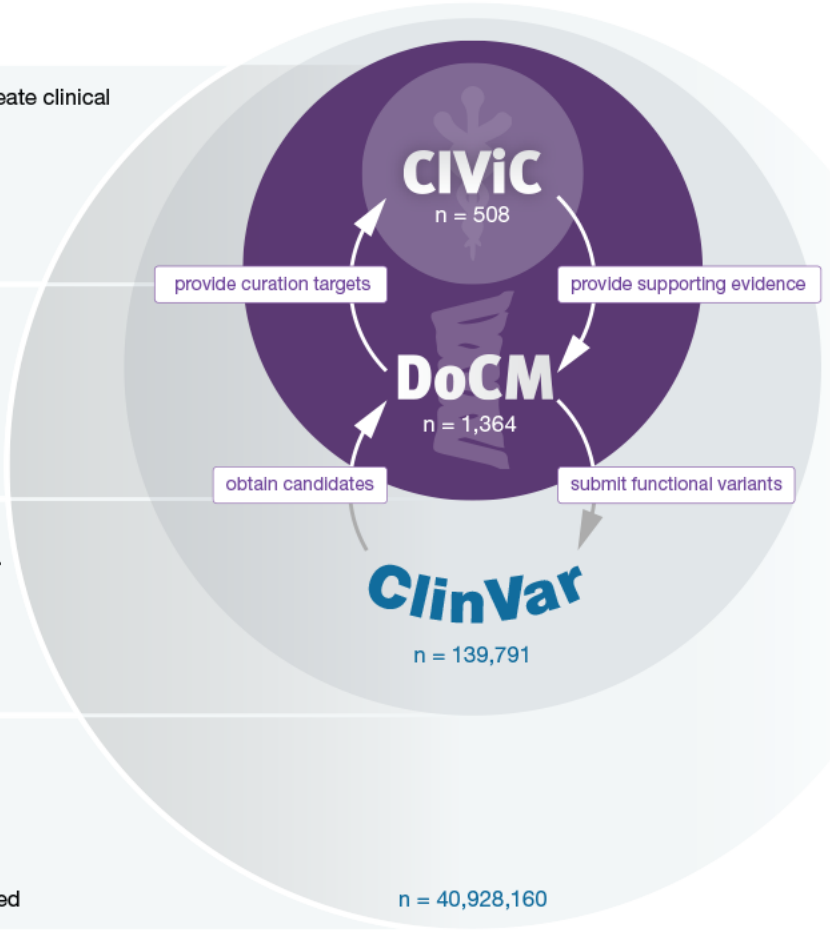
Record count: Millions
Curation burden: Low

ICGC, COSMIC and **TCGA** aggregates all variants observed in human cancer.

Curation Input: Published dataset
Disease Focus: Cancer
Curation product: Variant observations
License: Mixed
API: Mixed

DISCOVERY

* benign to pathogenic classification



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CIViC

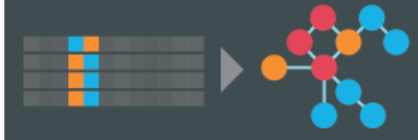
Data and Knowledge Production

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

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

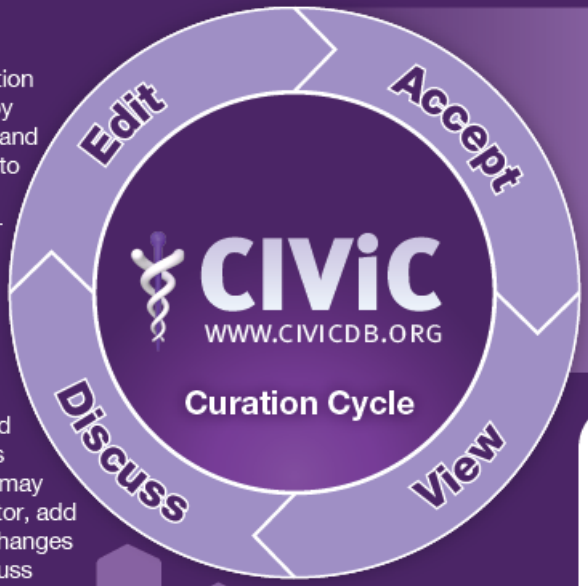
Data are reviewed and validation experiments performed to identify high quality events.

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

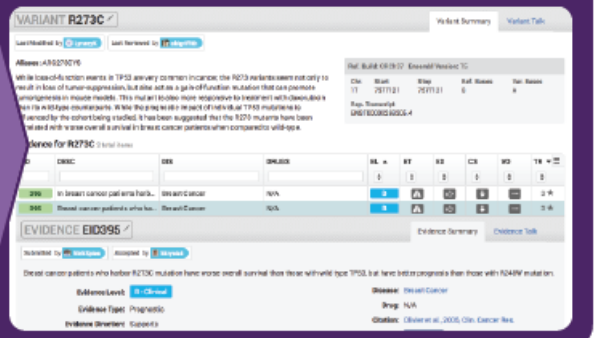


CIViC Curation

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.



Research Gene, Variant, & Evidence Summaries

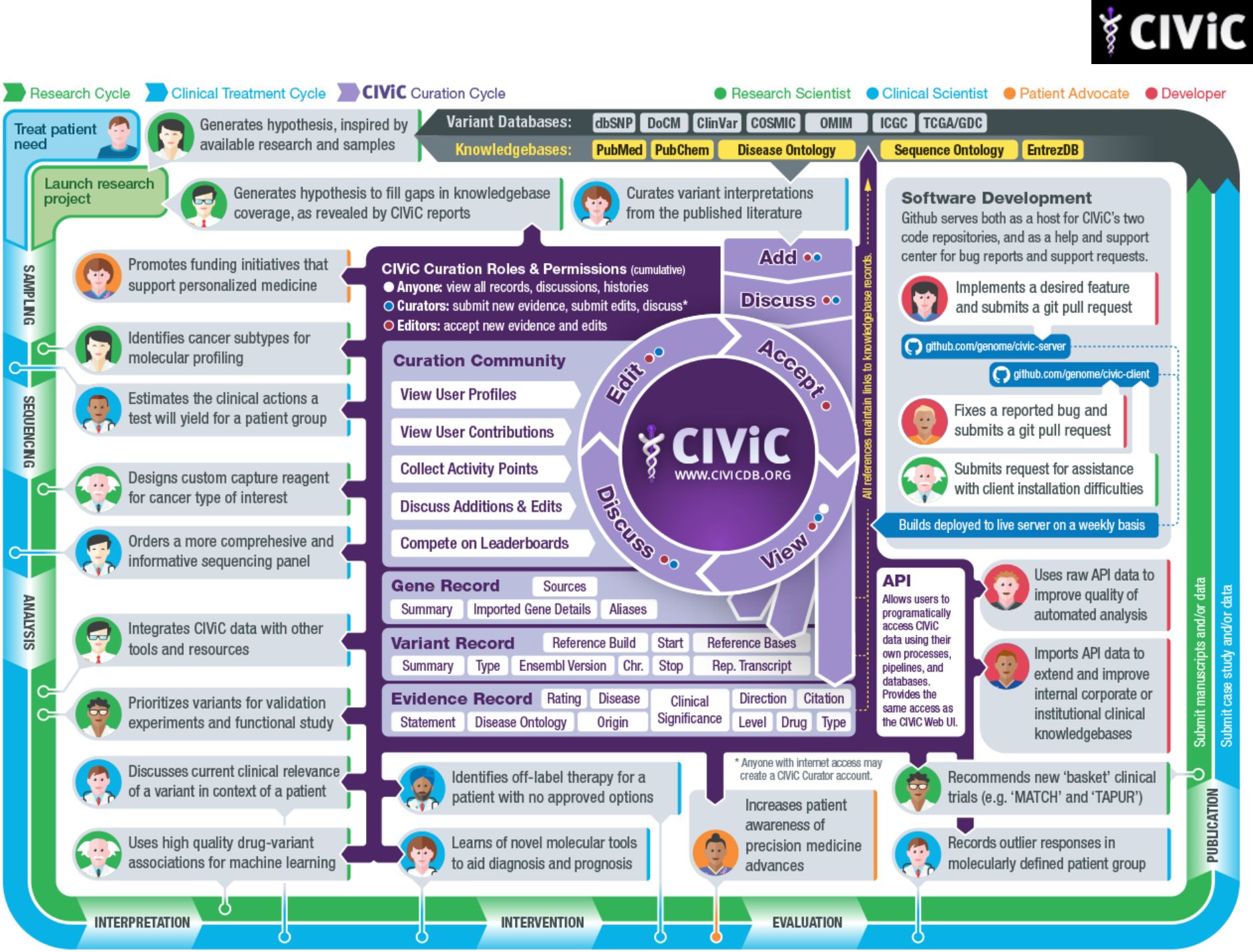


Add New Evidence

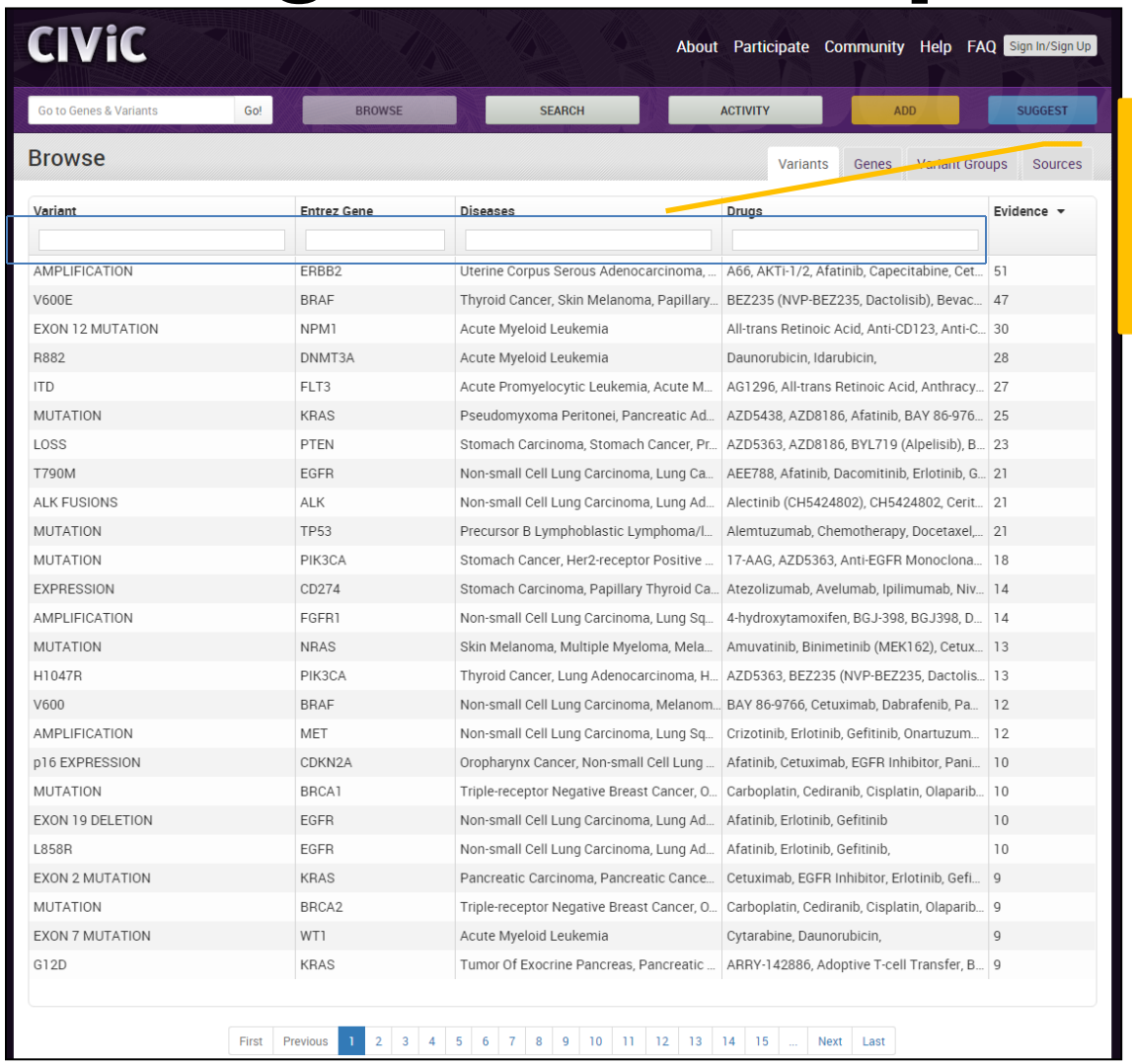
Review and Discuss Edits

A genome analyst uses CIViC's summaries to interpret and prioritize functionally significant events in the context of published literature, clinical trials, and linked knowledgebases.

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


CIViC
Research Cycle
Clinical Treatment Cycle
CIViC Curation Cycle
Research Scientist
Clinical Scientist
Patient Advocate
Developer
Treat patient need
Generates hypothesis, inspired by available research and samples
Variant Databases:
dbSNP
DoCM
ClinVar
COSMIC
OMIM
ICGC
TCGA/GDC
Knowledgebases:
PubMed
PubChem
Disease Ontology
Sequence Ontology
EntrezDB
Launch research project
Generates hypothesis to fill gaps in knowledgebase coverage, as revealed by CIViC reports
Curates variant interpretations from the published literature
Software Development
Github serves both as a host for CIViC's two code repositories, and as a help and support center for bug reports and support requests.
Implements a desired feature and submits a git pull request
github.com/genome/civic-server
github.com/genome/civic-client
Fixes a reported bug and submits a git pull request
Submits request for assistance with client installation difficulties
Builds deployed to live server on a weekly basis
SAMPLING
Promotes funding initiatives that support personalized medicine
Identifies cancer subtypes for molecular profiling
SEQUENCING
Estimates the clinical actions a test will yield for a patient group
Designs custom capture reagent for cancer type of interest
Orders a more comprehesive and informative sequencing panel
ANALYSIS
Integrates CIViC data with other tools and resources
Prioritizes variants for validation experiments and functional study
Discusses current clinical relevance of a variant in context of a patient
Uses high quality drug-variant associations for machine learning
CIViC Curation Roles & Permissions (cumulative)
Anyone: view all records, discussions, histories
Curators: submit new evidence, submit edits, discuss*
Editors: accept new evidence and edits
Add
Discuss
Curation Community
View User Profiles
View User Contributions
Collect Activity Points
Discuss Additions & Edits
Compete on Leaderboards
Edit
Accept
Discuss
View
CIViC
WWW.CIVICDB.ORG
All references maintain links to knowledgebase records.
Gene Record
Sources
Summary
Imported Gene Details
Aliases
Variant Record
Reference Build
Start
Reference Bases
Summary
Type
Ensembl Version
Chr.
Stop
Rep. Transcript
Evidence Record
Rating
Disease
Clinical Significance
Direction
Citation
Statement
Disease Ontology
Origin
Level
Drug
Type
API
Allows users to programatically access CIViC data using their own processes, pipelines, and databases. Provides the same access as the CIViC Web UI.
Uses raw API data to improve quality of automated analysis
Imports API data to extend and improve internal corporate or institutional clinical knowledgebases
Identifies off-label therapy for a patient with no approved options
Learns of novel molecular tools to aid diagnosis and prognosis
* Anyone with internet access may create a CIViC Curator account.
Increases patient awareness of precision medicine advances
Recommends new 'basket' clinical trials (e.g. 'MATCH' and 'TAPUR')
Records outlier responses in molecularly defined patient group
Submit manuscripts and/or data
Submit case study and/or data
PUBLICATION
INTERPRETATION
INTERVENTION
EVALUATION

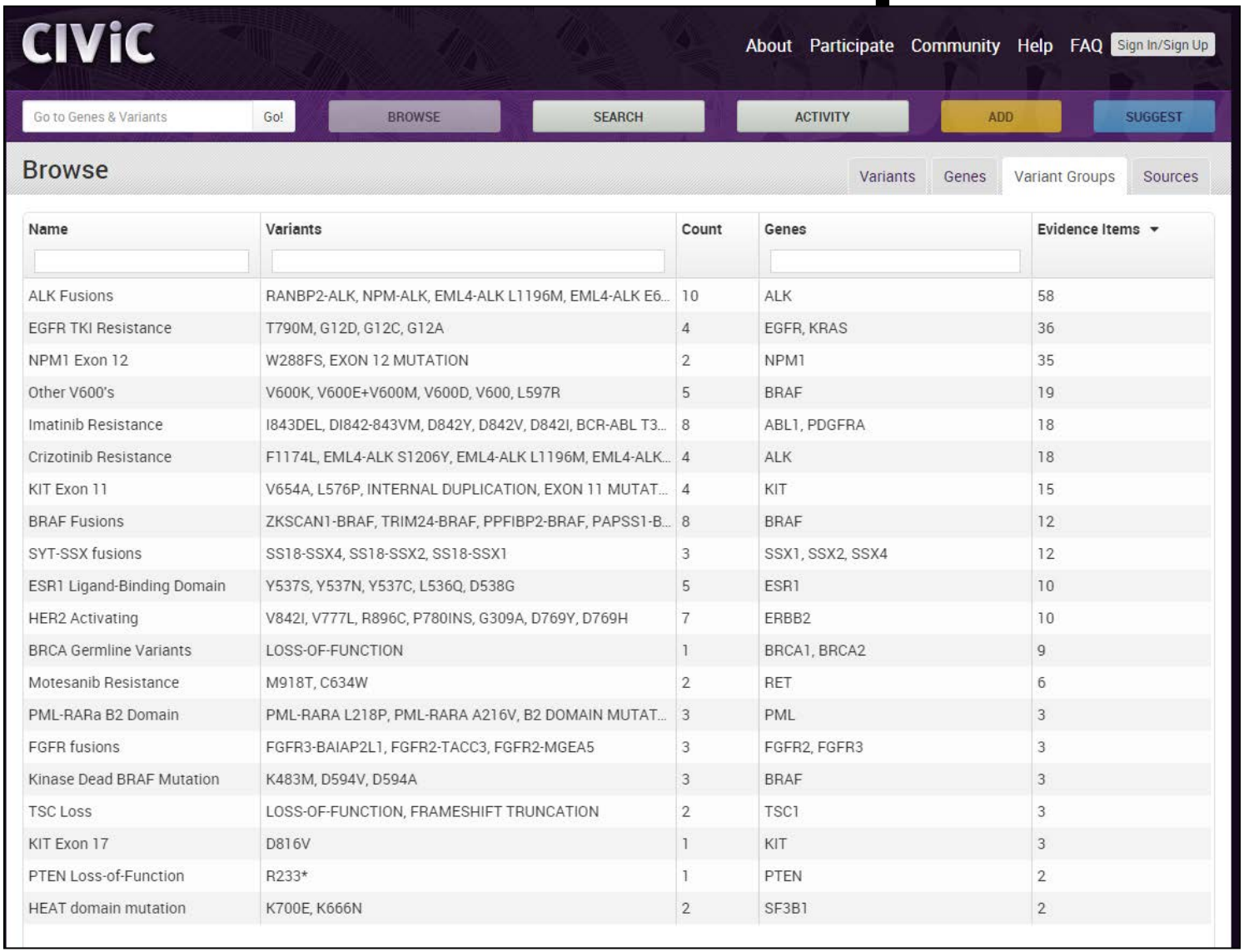
Using ‘Browse’ Option



Variant	Entrez Gene	Diseases	Drugs	Evidence
AMPLIFICATION	ERBB2	Uterine Corpus Serous Adenocarcinoma, ...	A66, AKTi-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 Monoclona...	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, Pani...	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

Various Search Criteria on Variants and Genes tabs

Variant Groups



CIViC

About Participate Community Help FAQ Sign In/Sign Up

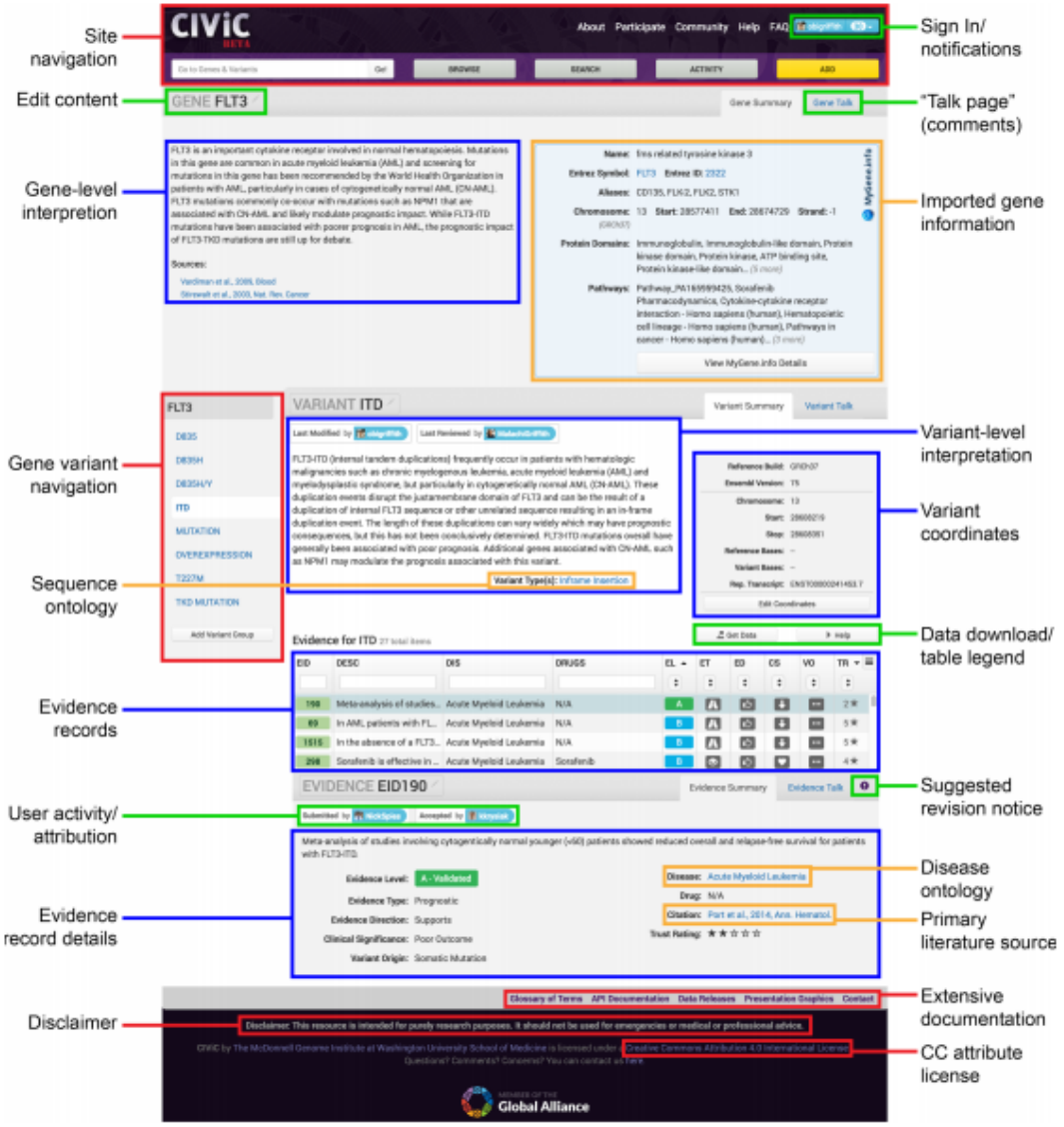
Go to Genes & Variants | Go! | BROWSE | SEARCH | ACTIVITY | ADD | SUGGEST

Browse

Variants | Genes | Variant Groups | Sources

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, DI842-843VM, 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

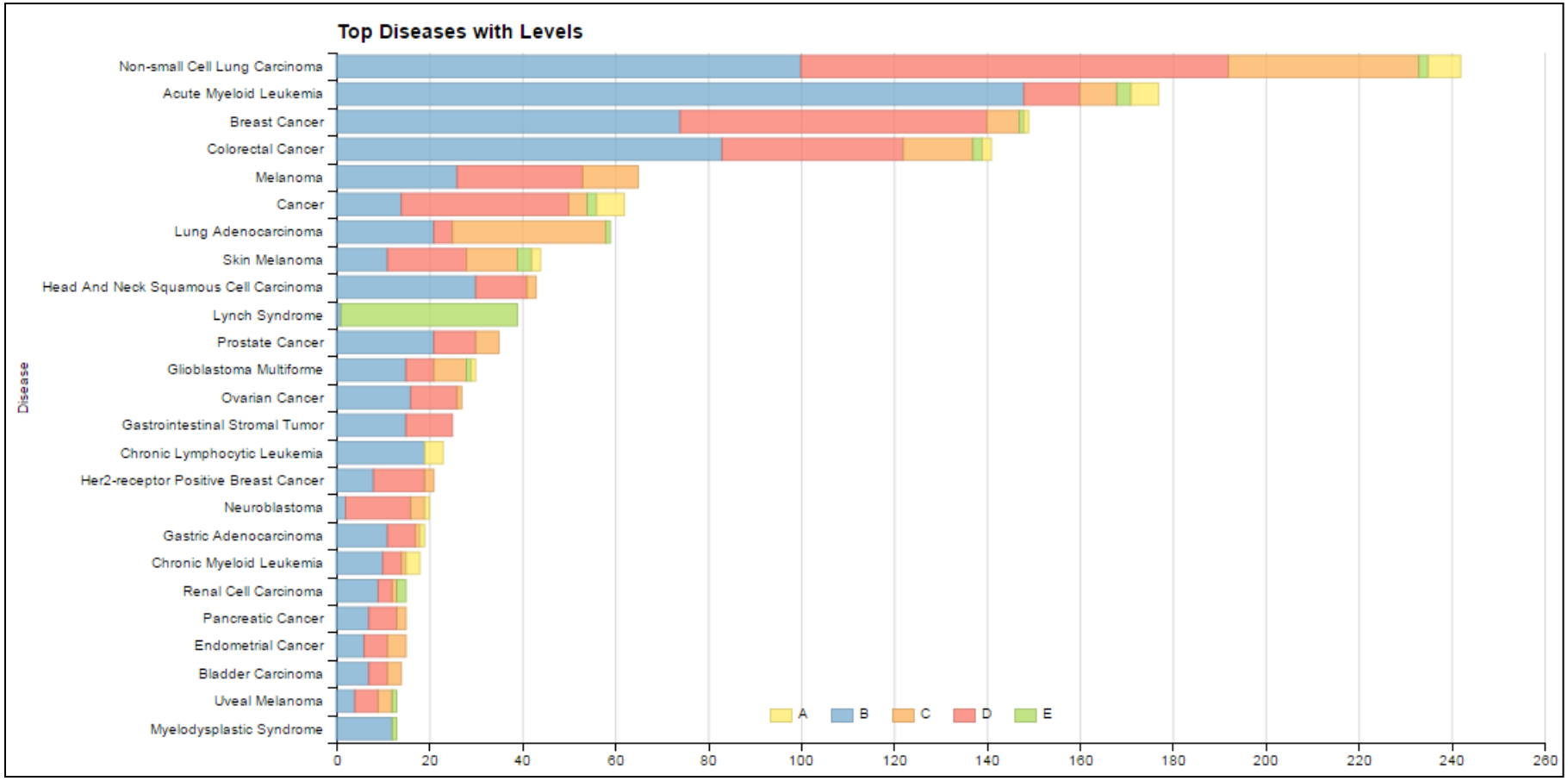
Gene Page


Site navigation
Edit content
Gene-level interpretion
Gene variant navigation
Sequence ontology
Evidence records
User activity/ attribution
Evidence record details
Disclaimer
Sign In/ notifications
"Talk page" (comments)
Imported gene information
Variant-level interpretation
Variant coordinates
Data download/ table legend
Suggested revision notice
Disease ontology
Primary literature source
Extensive documentation
CC attribute license
CIViC
About Participate Community Help FAQ
GENE FLT3
VARIANT ITD
Evidence for ITD
EVIDENCE EID190
Global Alliance

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?

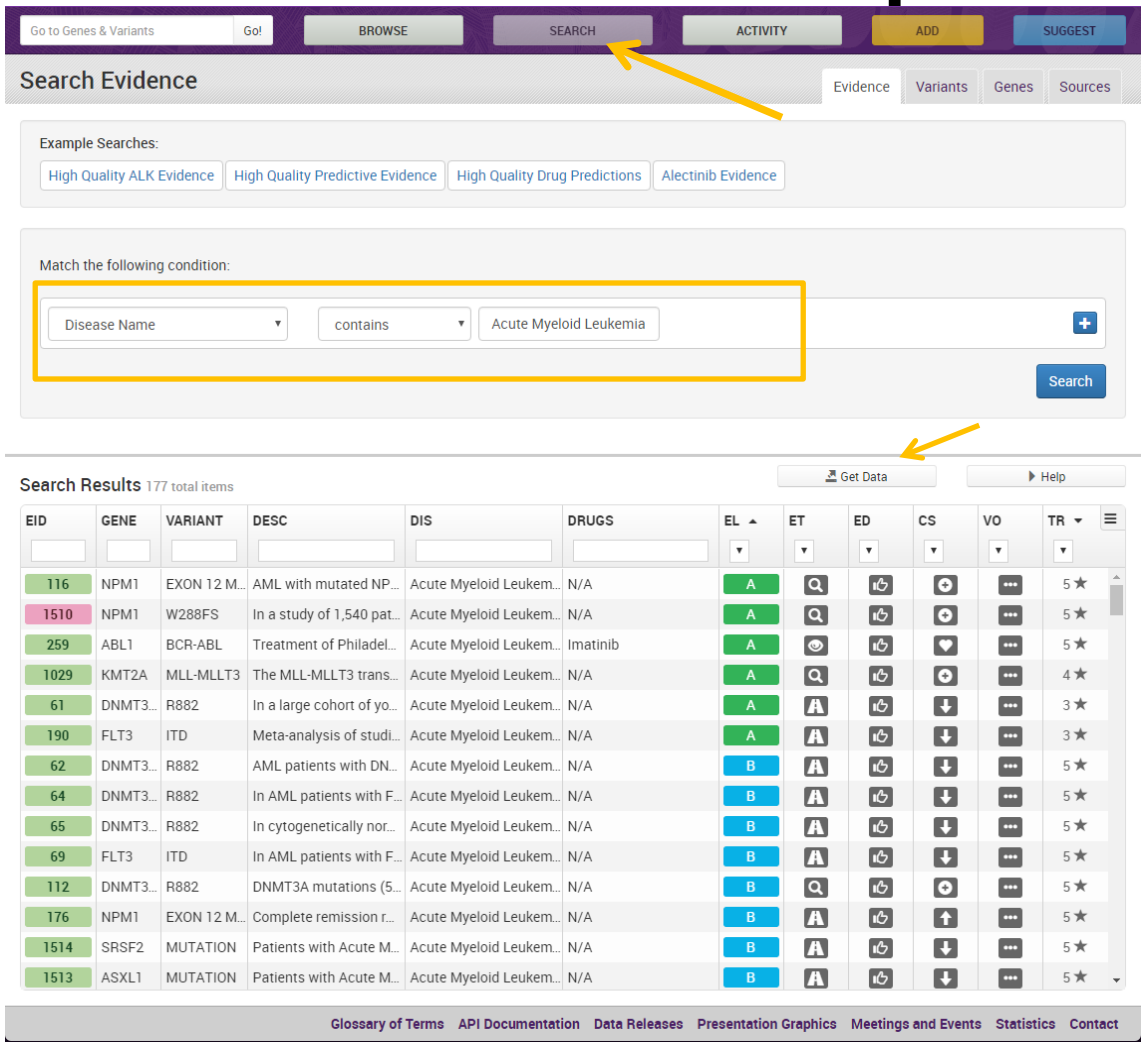


* Click on “Statistics” link at bottom of home page to see this bar graph and other data.

Scenario #1

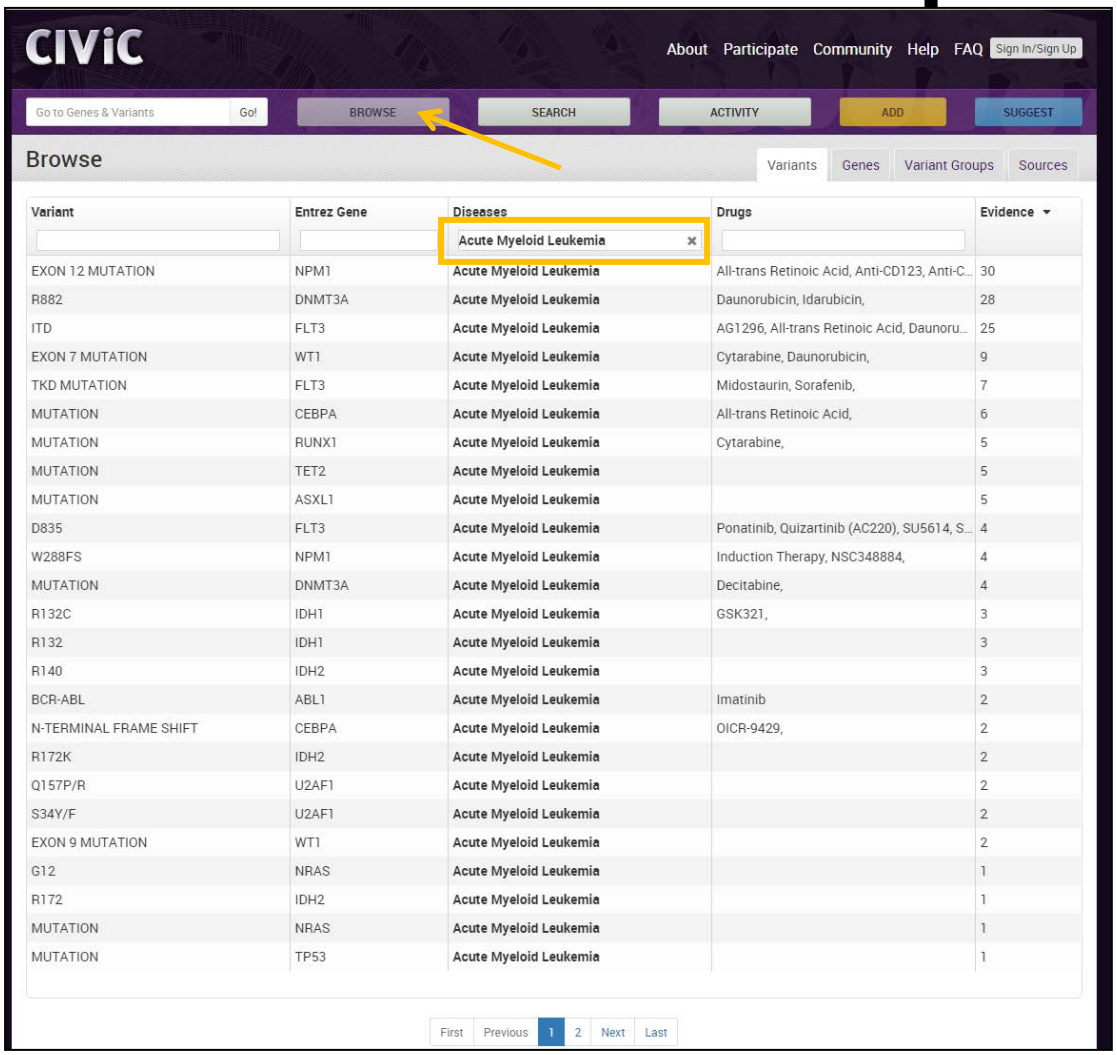
- You are a laboratory professional designing new disease specific clinical NGS panels.
  - What genes do you include in your Acute Myeloid Leukemia panel?
  - What diseases are best supported by CIViC?

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



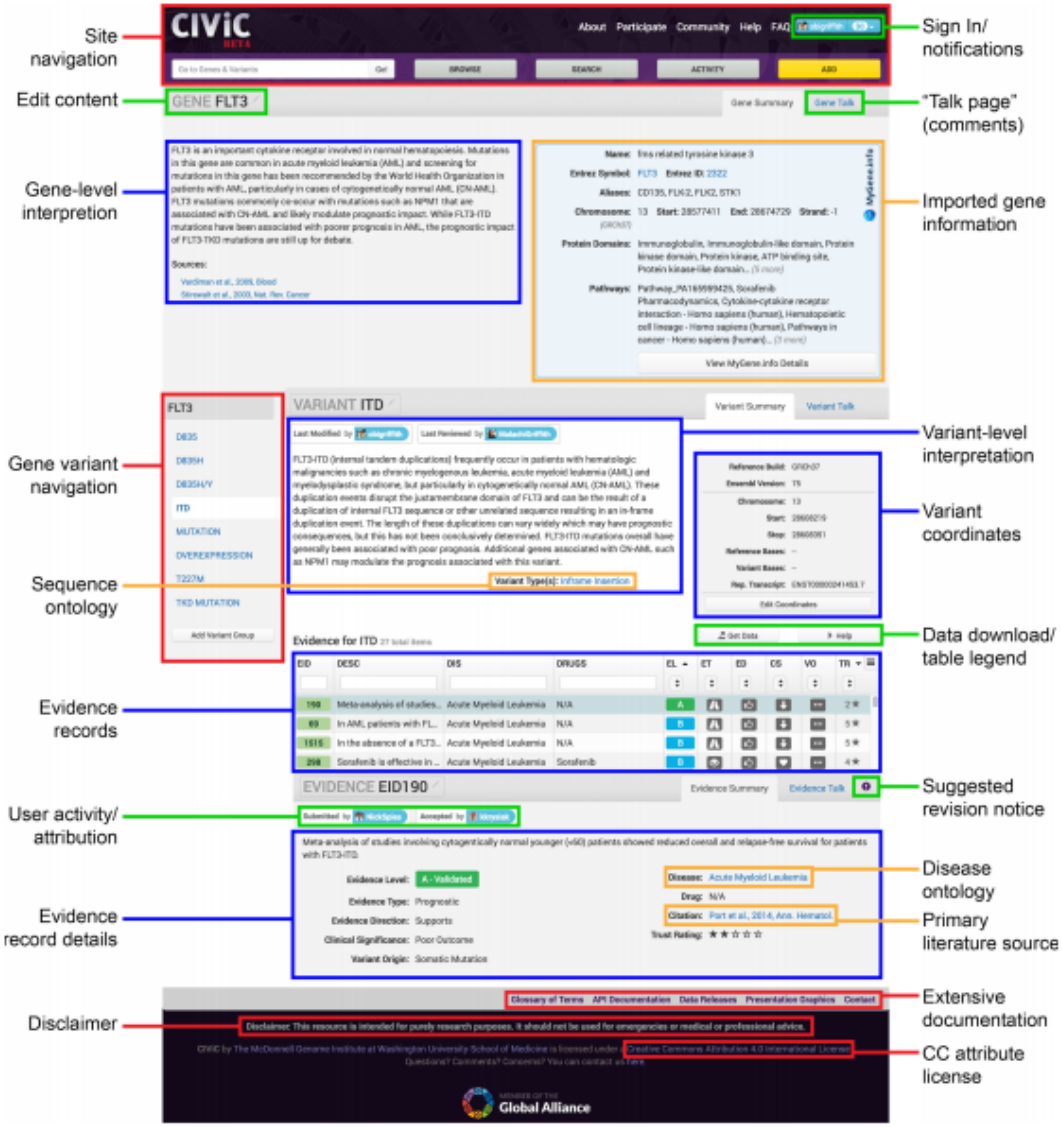
- Using “Search” match the disease name to your disease of interest under the ‘Evidence’ tab
- Can export data from table as .CSV
- Select any gene/variant from the list to view in more detail.

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

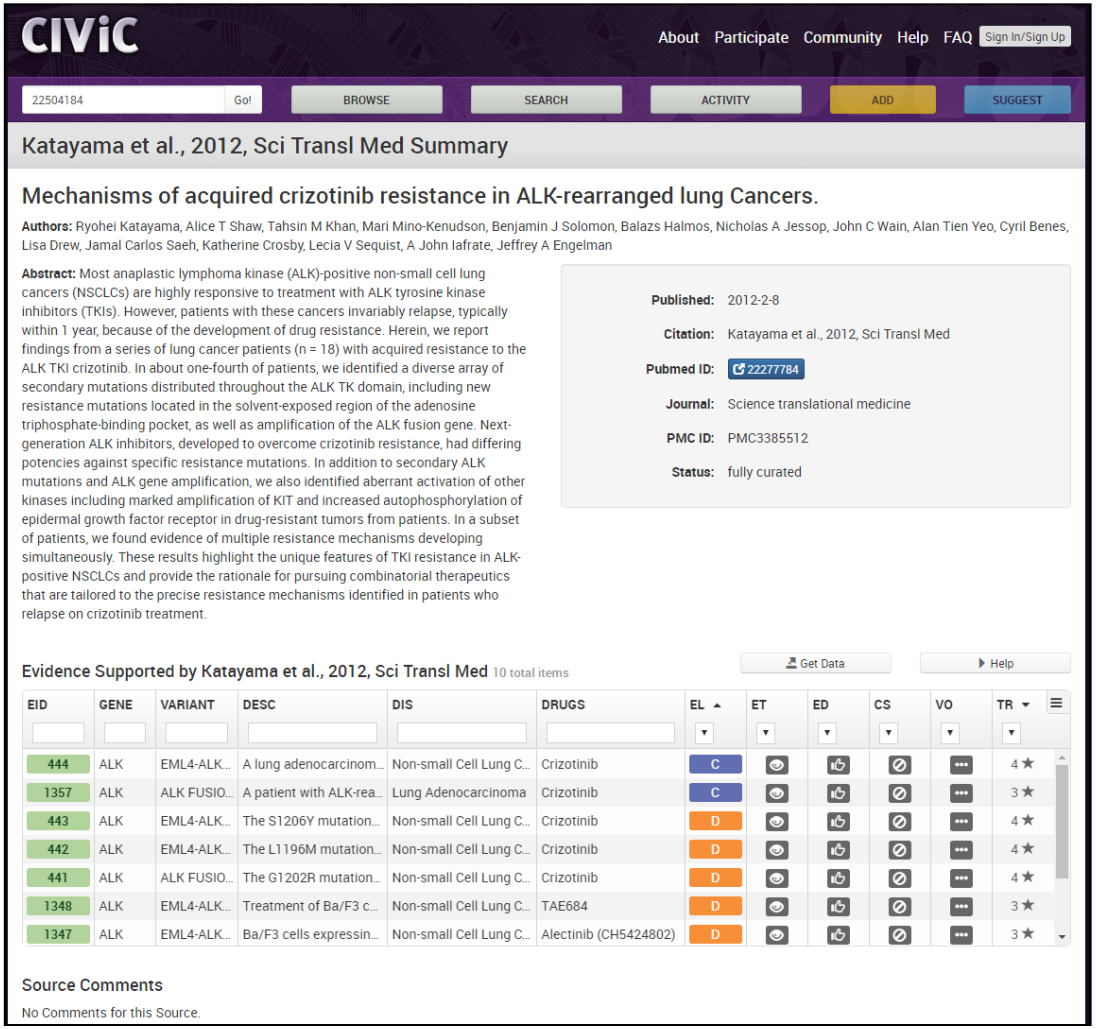


- Using "Browse", type in your disease of interest into the designated box in the variants tab or the genes tab.
- If you search under the genes tab, you won't have genes duplicated on the list but you lose variant information.
- Not able to export list as .CSV
- Select any gene/variant from the list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

Gene Page


Site navigation
Edit content
Gene-level interpretion
Gene variant navigation
Sequence ontology
Evidence records
User activity/ attribution
Evidence record details
Disclaimer
Sign In/ notifications
"Talk page" (comments)
Imported gene information
Variant-level interpretation
Variant coordinates
Data download/ table legend
Suggested revision notice
Disease ontology
Primary literature source
Extensive documentation
CC attribute license
CIViC
About Participate Community Help FAQ
GENE FLT3
Gene Summary
Gene Talk
VARIANT ITD
Variant Summary
Variant Talk
Evidence for ITD
EVIDENCE EID190
Evidence Summary
Evidence Talk
Glossary of Terms
API Documentation
Data Releases
Presentation Graphics
Contact
Disclaimer: This resource is intended for purely research purposes. It should not be used for emergencies or medical or professional advice.
Global Alliance

Reference back to PMID/other CIViC entries from same citation

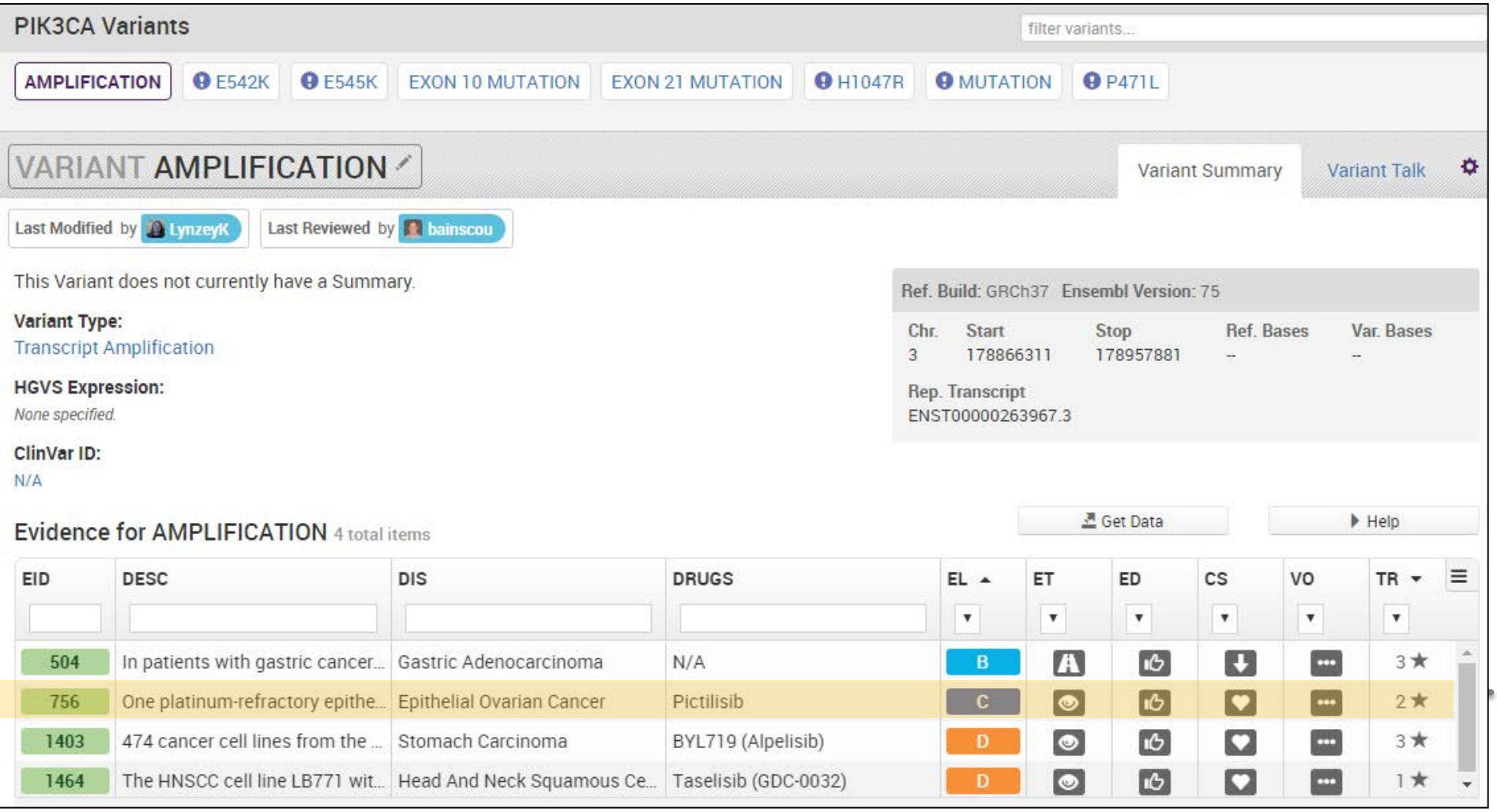


- Click on Citation link on bottom of gene/variant page.
- Evidence Summary page has article information and abstract
- List of Evidence items associated with primary publication near bottom of page.

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



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

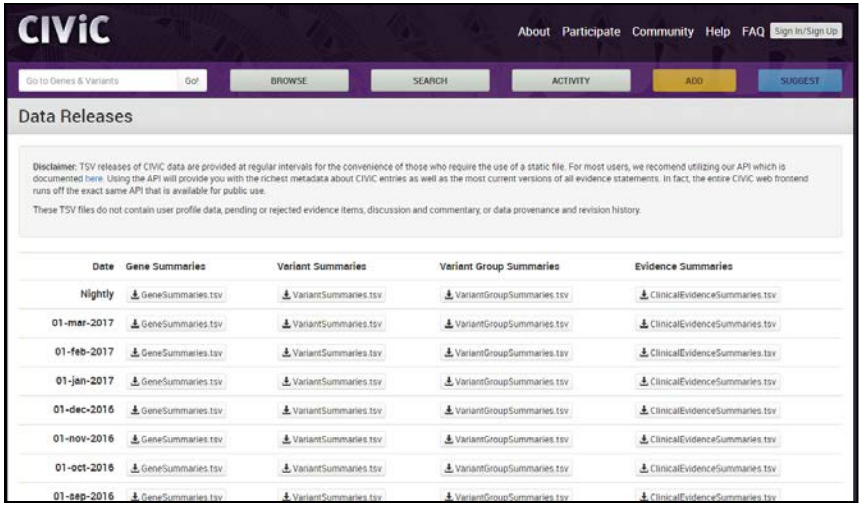
- You have been given the task of putting together a Pan Cancer List for your laboratory/institution.
  - Which genes should be included in your list?

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

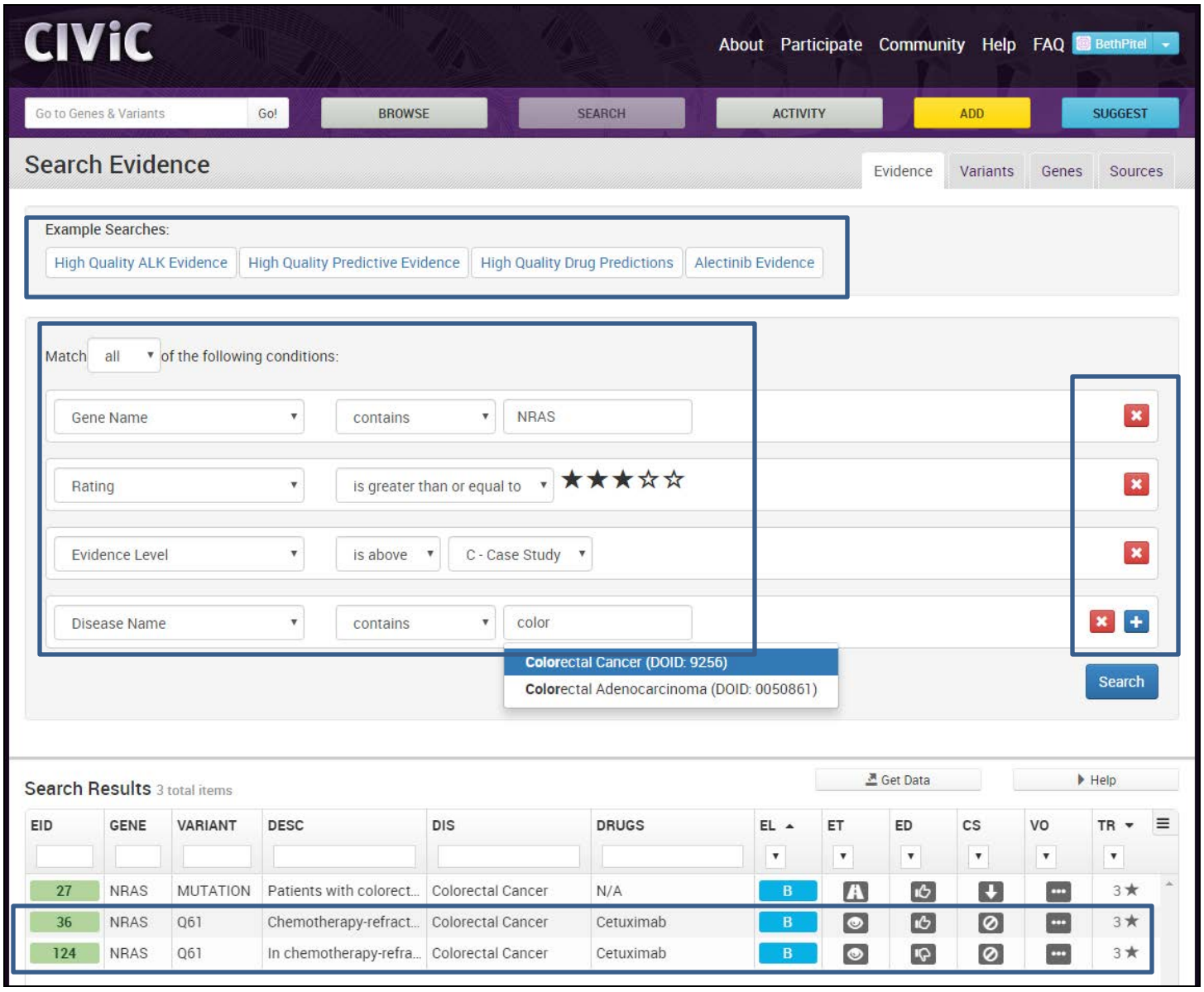
Download Data Release

- 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



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)



*** 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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