

ClinGen Somatic Cancer Variant Curation and Interpretation in CIViC

H3Africa-RDWG/ClinGen Workshop

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Coordinator, ClinGen Somatic Cancer Clinical Domain Working
Group

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THE INNOVATION CENTER FOR BIOMEDICAL INFORMATICS



ClinGen Somatic Cancer Clinical Domain Working Group (CDWG) Goals

- **Standardize** the curation and interpretation of somatic variants in cancer by the uniform implementation of guidelines
- **Collaborate** with expert groups to develop processes that support accurate determination of the clinical significance of somatic changes for use by physicians, clinical laboratories and researchers
- **Enhance the usability, dissemination and implementation** of cancer somatic changes in the ClinGen resource & other knowledgebases including CIViC, ClinVar, GA4GH VICC-metaKB and Virtual Molecular Tumor Boards





Summary of Somatic Cancer CDWG

Membership

>100 Members

>30
Organizations

*Communities/
Consortiums
engaged*

Academic
Medical
Centers

LDT
developers

NCI, FDA

GA4GH/VICC,
CIViC

AMIA

AMP/CAP/
ACMG/ASCO

Disease Taskforces

Pediatric
Cancers

Hematological
Cancers

Genitourinary
Cancers

Somatic Cancer Variant Curation Expert Panels (SC-VCEP)

NTRK fusions
*(Step 1
approved)*

FLT3
*(Currently
Forming)*

FGFR genes
*(Currently
Forming)*





Somatic Cancer CDWG Team

<https://clinicalgenome.org/working-groups/somatic/>

Chairs



Shashikant Kulkarni, PhD



Subha Madhavan, PhD

Coordinators



Shruti Rao, MS, MBA

Disease Taskforce and Informatics Leadership



Gordana Raca, PhD



**Angshumoy Roy, M.B.B.S.,
Ph.D.**



Xinjie Xu, PhD., FACMG



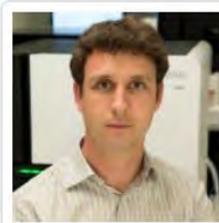
**Rashmi Kanagal-
Shamanna**



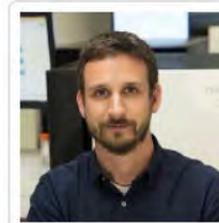
Ian King, PhD, FACMG



**Shamini Selvarajah, PhD,
DABMGG, FACMGG,
FCCMG**



Obi Griffith, PhD



Malachi Griffith, PhD



Alex Wagner, PhD



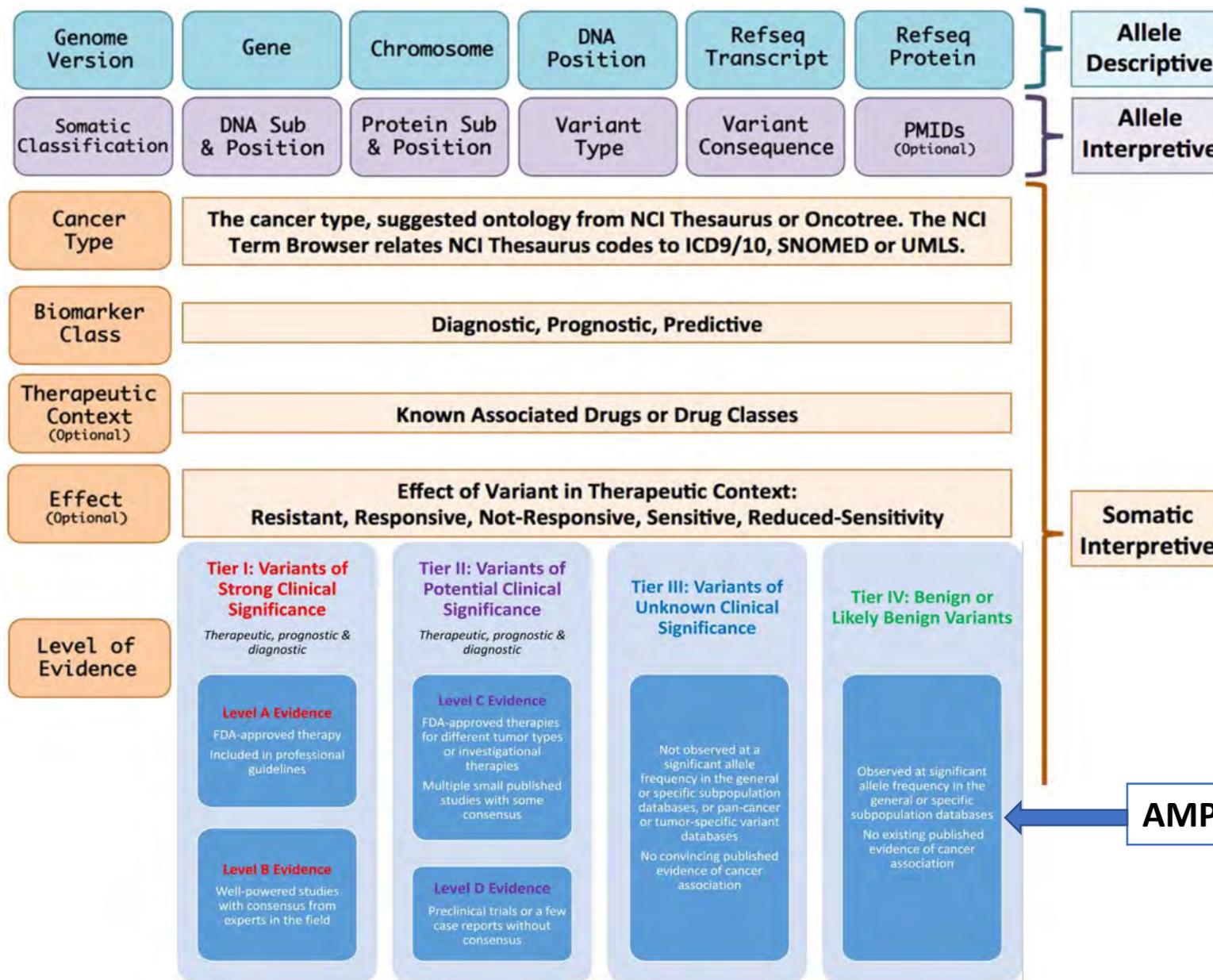
Somatic Cancer Disease Taskforces

Curation Goals

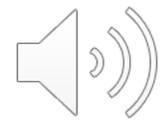
Disease Taskforces	Co-Leads	# of Members	Taskforce formed in	Taskforce Goals
Pediatric Cancers	<ul style="list-style-type: none">• Angshumoy Roy• Gordana Raca	~54	2017	<i>Variant curation for ~44 highly relevant pediatric cancer genes across 23 tumor types (e.g. CTNNB1, IKZF1, TP53, SMARCA4, SMARCB1, ABL1 fusions etc.)</i>
Hematologic Cancers	<ul style="list-style-type: none">• Rashmi Kanagal-Shamana• Xinjie Xu	~43	2020	<i>Variant Curation of FLT3 TKD mutations, BCR/ABL1 kinase domain mutations, BCL2 mutations associated with venetoclax resistance</i>
<i>Fusion curation in Ph-like B-ALL (collaboration b/w pediatric and hematologic cancers TF)</i>				
Genitourinary Cancers	<ul style="list-style-type: none">• Shamini Selvarajah• Ian King	~12	2020	<i>Variant curation of FGFR genes</i>



Minimum Variant Level Data (MVLD) (Ritter DI, et al.2016) mapped to AMP/ASCO/CAP guidelines (Li M, et al. 2017)



AMP/ASCO/CAP guidelines



ClinGen Somatic Cancer CDWG uses CIViC as its data curation platform

www.civicdb.org

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

Search Evidence

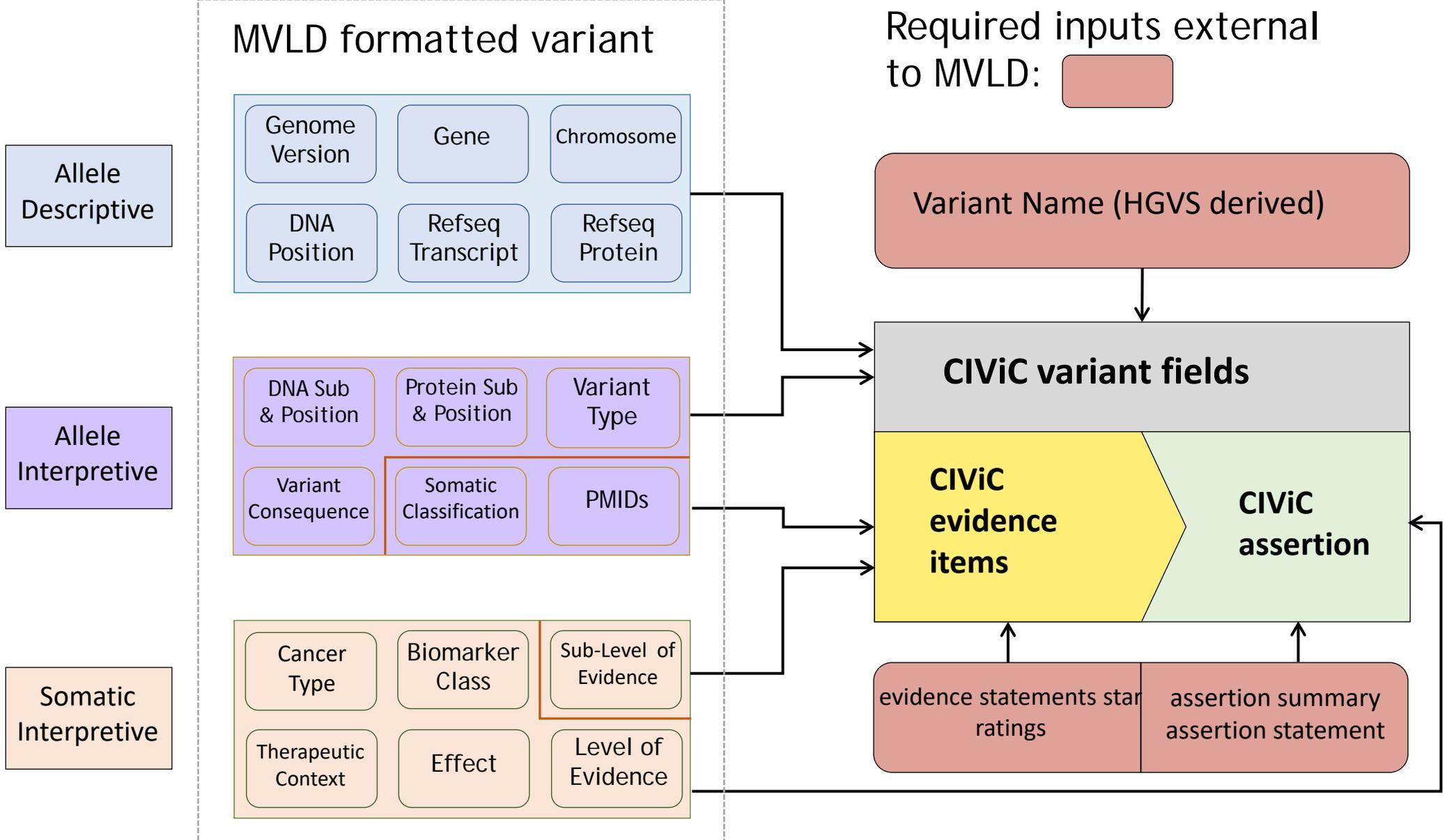
Evidence **Assertions** Variants Genes Sources Suggested Changes

Search Results 183 total items

EID	GENE	VARIANT	DIS	DRUGS	DESC	EL	ET	ED	CS	VO	ER
6449	H3-3A	K27M	Glioblastoma Multiforme	N/A		B	Q	👍	⊗	⋮	4★
6463	H3-3B	K36M	Chondroblastoma	N/A		B	Q	👍	+	⋮	4★
6469	H3-3A	G34W	Bone Giant Cell Tumor	N/A		B	Q	👍	+	⋮	4★
7008	NCOA2	HEY1-NCO...	Mesenchymal Chondrosarco...	N/A		B	Q	👍	+	⋮	4★
7009	FOXO1	PAX3-FOX...	Alveolar Rhabdomyosarcoma	N/A		B	Q	👍	+	⋮	4★
7010	FOXO1	PAX7-FOX...	Alveolar Rhabdomyosarcoma	N/A		B	Q	👍	+	⊗	4★
7189	H3-3A	MUTATION	Pediatric Low-grade Glioma (...)	N/A		B	A	👍	↓	⋮	4★
7190	ATRX	DELETION	Pediatric Low-grade Glioma (...)	N/A		B	A	👍	↓	⋮	4★
7191	BRAF	V600E	Pediatric Low-grade Glioma (...)	N/A		B	A	👍	↓	⋮	4★
7192	CDKN2A	DELETION	Pediatric Low-grade Glioma (...)	N/A		B	A	👍	↓	⋮	4★
7193	BRAF	KIAA1549-...	Pediatric Low-grade Glioma (...)	N/A		B	A	👍	↑	⋮	4★
7194	MYB	AMPLIFIC...	Pediatric Low-grade Glioma (...)	N/A		B	A	👍	↑	⋮	4★
7203	FGFR1	INTERNAL...	Pediatric Low-grade Glioma (...)	N/A		B	Q	👍	+	⋮	4★



Mapping of MVLD and AMP/ASCO/CAP guidelines into CIViC Fields



ClinGen Somatic Cancer Variant Curation Process

Somatic Cancer CDWG disease taskforces prioritize genes-variants for curation

Perform variant literature search
(PubMed full text, ASCO abstracts, Google Scholar, CIViCmine, eGARD)

Curate and submit variant evidence in CIViC from PubMed articles and ASCO abstracts using CIViC evidence levels

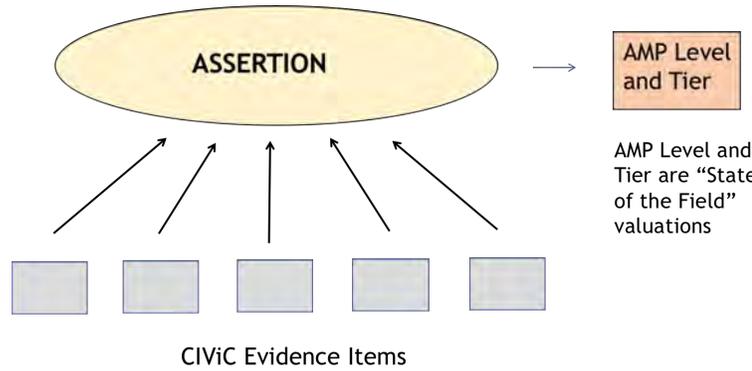
Curate and submit variant assertion in CIViC using AMP/ASCO/CAP guidelines

E.g. EGFR L858R in NSCLC Supports Sensitivity/Response to Erlotinib

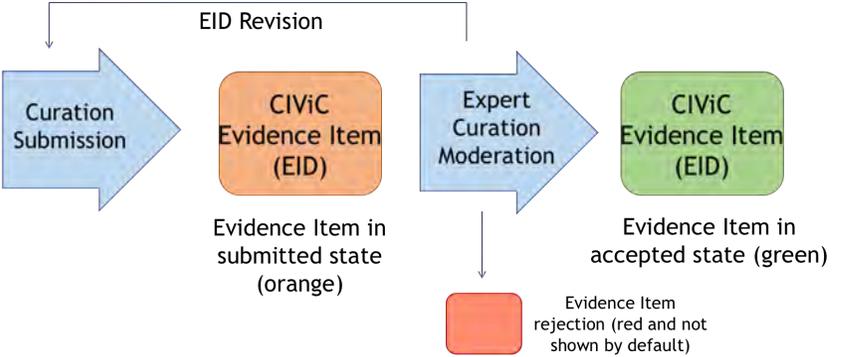
Evidence/Assertion reviewed and accepted by ClinGen-CIViC editors

Evidence/Assertion finalized and approved by ClinGen Somatic Expert Panels

Curations will be converted and submitted to ClinVar

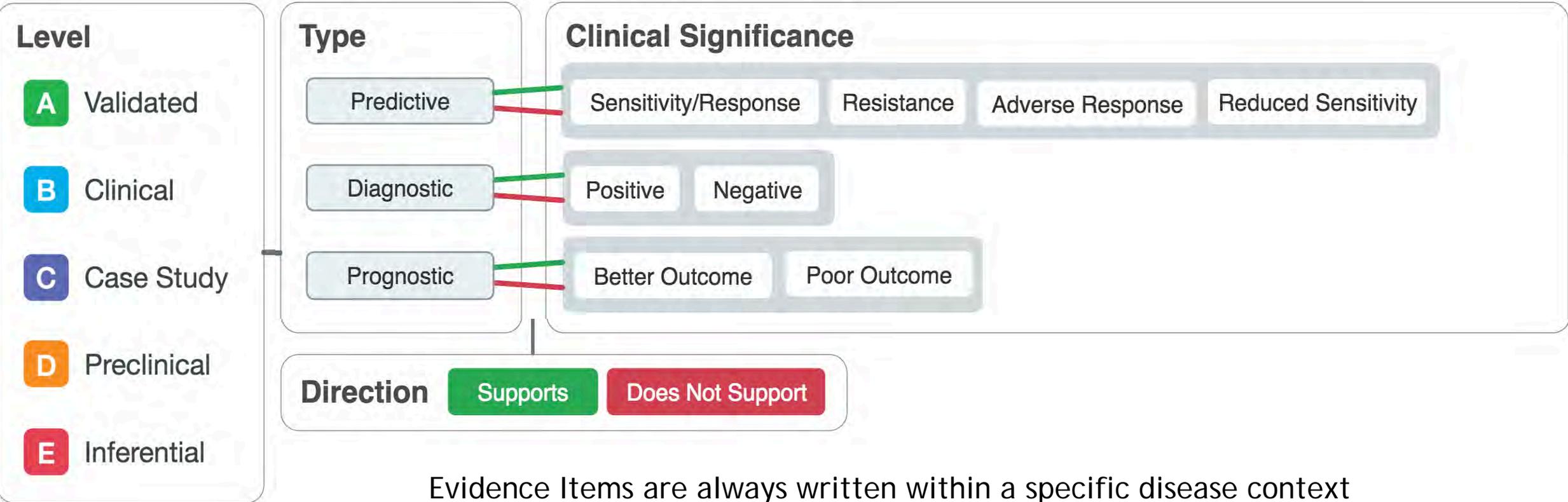


E.g. EGFR L858R in NSCLC Supports Sensitivity/Response to Erlotinib, AMP Tier IA evidence



EID	GENE	VARIANT	DIS	DRUGS	DESC	EL	ET	ED	CS	VO	ER
6449	H3-3A	K27M	Oligioblastoma Multiforme	N/A		B					
6463	H3-3B	K36M	Chondroblastoma	N/A		B					

Structure of the CIViC Evidence Item (EID)



Examples:

- “EGFR L858R in NSCLC Supports Sensitivity/Response to Erlotinib”
- “EGFR T790M in NSCLC Supports Resistance to Erlotinib”
- A KRAS mutation in colorectal cancer in a patient who does respond to EGFR monoclonal ab inhibition would receive a “does not support resistance” annotation



Example of Adding Predictive Evidence Type in CIViC from the Anderson et al. paper below

Clinical Trial > Blood. 2017 Jun 22;129(25):3362-3370. doi: 10.1182/blood-2017-01-763003.

Epub 2017 May 4.

Clinicopathological features and outcomes of progression of CLL on the BCL2 inhibitor venetoclax

Mary Ann Anderson ^{1 2 3 4}, Constantine Tam ^{3 4 5}, Thomas E Lew ², Surender Juneja ^{1 4},
Manu Juneja ², David Westerman ^{4 5}, Meaghan Wall ^{3 6 7}, Stephen Lade ^{4 5},
Alexandra Gorelik ⁸, David C S Huang ^{2 3}, John F Seymour ^{3 4 5}, Andrew W Roberts ^{1 2 3 4}

Affiliations + expand

PMID: 28473407 DOI: 10.1182/blood-2017-01-763003



SOURCE: <https://pubmed.ncbi.nlm.nih.gov/28473407/>



Somatic Cancer Variant Curation Training Materials

<https://clinicalgenome.org/curation-activities/somatic/>



Get Started About Us- **Curation Activities** Working Group Training Modules Additional Supporting Materials

Gene-Disease Validity

- » Training Materials
- » Browse Curations

Training Materials

Training videos and SOP documents available for those interested in Somatic Variant Curation.

[Learn More](#)

Documents

Documents
Variant Curation

[Learn More](#)

Somatic Variant Curation Interface

- Click on the Sign In/ Sign Up button on the Top Right of the webpage
- You can sign-in using your Google ID, ORCID or GitHub ID
- Email CIViC help@civicdb.org and request them to associate your account with the ClinGen Somatic Organization

[Sign In/Sign Up](#)

Recommended

1 CIVIC - Getting Started

This video covers: Description of CIViC and its goals, Navigating through CIViC's core pages, Browsing, searching, and consuming knowledgebase content.

[→ CIVIC - Getting Started](#)

[Start →](#)

Recommended

2 CIVIC - Adding Evidence

This video covers: Scanning a publication for curatable details, Signing into CIViC to Add Evidence, Walking through the Add Evidence form, Viewing the submitted evidence.

[→ Adding Evidence to CIViC](#)

[Start →](#)

Recommended

3 CIVIC - Editing Entities

This video covers: a brief introduction to editorial review and revision of a submitted evidence record in CIViC (civicdb.org).

[→ CIVIC - Editing Entities](#)

[Start →](#)

Recommended

4 CIVIC - Adding Source Suggestions

This video covers: how a CIViC user can suggest a source listed in PubMed, how to find the CIViC Source Suggestions queue, and how to communicate with other CIViC users with comments.

[→ CIVIC - Adding Source Suggestions](#)

[Start →](#)

5

Recommend

Somatic cancer variant curation and harmonization through consensus minimum variant level data

[→ Somatic cancer variant curation and harmonization through consensus minimum variant level data](#)

[Start →](#)

6

Recommended

The CIViC Knowledge Model and Standard Operating Procedures for Curation and Clinical Interpretation of Variants in Cancer

[→ The CIViC Knowledge Model and Standard Operating Procedures for Curation and Clinical Interpretation of Variants in Cancer](#)

[Start →](#)





ClinGen Somatic Cancer CDWG curation activities in CIViC

Organization



ClinGen

Actions	Last Action	Members
2,028	6 days ago	85

[Organization Website](#)



Pediatric Cancer Task Force at ClinGen

Actions	Last Action	Members
9,094	about 4 hours ago	35

[Organization Website](#)



Hematologic Cancer Taskforce at ClinGen

Actions	Last Action	Members
8,840	about 4 hours ago	31

[Organization Website](#)



Genitourinary Cancer Taskforce at ClinGen

Actions	Last Action	Members
7,382	about 4 hours ago	13

[Organization Website](#)



NTRK VCEP at ClinGen

Actions	Last Action	Members
5,403	a day ago	8

[Organization Website](#)

- 459 Evidence items associated with ~150 variants in prioritized genes entered in CIViC
- 16 Somatic variant assertions using AMP/ASCO/CAP guidelines
- ~85 ClinGen Somatic CDWG members have curator accounts in CIViC

Organization Statistics

Comments: 124	Submitted Evidence: 459
Suggested Revisions: 323	Accepted Evidence: 177
Applied Revisions: 193	Submitted Assertions: 16
Suggested Sources: 65	Accepted Assertions: 1



To join the Somatic Cancer CDWG please contact complete the ClinGen Volunteer Survey and indicate your interest in joining the appropriate ClinGen curation efforts

<https://clinicalgenome.org/working-groups/c3/>

ClinGen Community Curation (C3)

The mission of the ClinGen Community Curation WG (C3) is to engage, identify, and communicate with potential ClinGen volunteers, and to facilitate the organization and placement of volunteers in curation efforts.

Tools

Membership

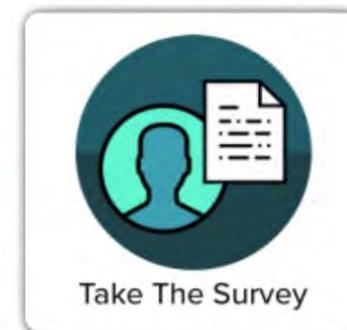


Seeking volunteers

Interested in volunteering for curation efforts **take our survey!**

If you have any questions, please feel free to email us at volunteer@clinicalgenome.org

Current Comprehensive Curation Efforts Accepting Volunteers



Chairs

Courtney Thaxton, PhD

Coordinators

Please contact a coordinator if you have questions.

Brooke Palus, M.S.

brooke_palus@med.unc.edu

