CIViCpy: A Python Software Development and Analysis Toolkit for the CIViC Knowledgebase

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PURPOSE Precision oncology depends on the matching of tumor variants to relevant knowledge describing the clinical significance of those variants. We recently developed the Clinical Interpretations for Variants in Cancer (CIViC; civicdb.org) crowd-sourced, expert-moderated, and open-access knowledgebase. CIViC provides a structured framework for evaluating genomic variants of various types (eg, fusions, single-nucleotide variants) for their therapeutic, prognostic, predisposing, diagnostic, or functional utility. CIViC has a documented application programming interface for accessing CIViC records: assertions, evidence, variants, and genes. Third-party tools that analyze or access the contents of this knowledgebase programmatically must leverage this application programming interface, often reimplementing redundant functionality in the pursuit of common analysis tasks that are beyond the scope of the CIViC Web application.

METHODS To address this limitation, we developed CIViCpy (civicpy.org), a software development kit for extracting and analyzing the contents of the CIViC knowledgebase. CIViCpy enables users to query CIViC content as dynamic objects in Python. We assess the viability of CIViCpy as a tool for advancing individualized patient care by using it to systematically match CIViC evidence to observed variants in patient cancer samples.

RESULTS We used CIViCpy to evaluate variants from 59,437 sequenced tumors of the American Association for Cancer Research Project GENIE data set. We demonstrate that CIViCpy enables annotation of 1,200 variants per second, resulting in precise variant matches to CIViC level A (professional guideline) or B (clinical trial) evidence for 38.6% of tumors.

CONCLUSION The clinical interpretation of genomic variants in cancers requires high-throughput tools for interoperability and analysis of variant interpretation knowledge. These needs are met by CIViCpy, a software development kit for downstream applications and rapid analysis. CIViCpy is fully documented, open-source, and available free online.

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INTRODUCTION The use of massively parallel sequencing to profile the molecular composition of human tissues has become increasingly commonplace in the clinical setting to inform diagnosis and therapeutic strategy for patients’ tumors.1,2 This has led to an ever-growing body of biomedical literature describing the impact of tumor variants on disease progression and response to therapy, creating a bottleneck of expert review of relevant literature to construct a clinical report.3 The Clinical Interpretations for Variants in Cancer (CIViC) community knowledgebase (civicdb.org) is a platform for expert crowdsourcing the clinical interpretation of variants in cancer.4 To date, CIViC contains 6,471 interpretation evidence records (ie, clinical significance statements extracted from biomedical literature) describing 2,312 variants in 402 genes. Evidence in CIViC is used to construct interpretation assertions of clinical significance (ie, therapeutic, prognostic, diagnostic, or predisposing effects) of gene variants on the basis of published criteria and guidelines for the classification of variant interpretations.5,6 CIViC evidence and assertions are also linked to data classes describing genes, drugs (if applicable), and diseases, in addition to the myriad supporting data for tracking the provenance and community activity surrounding these concepts and their relationships. These data are released under a Creative Commons public domain attribution (CCO), promoting their redistribution and use in downstream applications.

As a curation platform for the Clinical Genome Resource (ClinGen) Somatic Working Group,7 CIViC supports the export of generated assertions to ClinVar, in line with existing ClinGen submission practices for
germline diseases. This was accomplished through the development of the civic2clinvar export utility and Python package, which constructs ClinVar-style submission records from CIViC assertions. In developing civic2clinvar, several issues with building an application from the CIViC database and application programming interface (API) were identified: (1) simplified retrieval and use of CIViC records as native Python objects, (2) routines for local caching of CIViC data for analysis, (3) support for high-throughput queries, and (4) export of CIViC records to established variant representation formats, such as variant call format (VCF).

Here, we describe CIViCpy, a software development kit (SDK) that addresses these needs and enables rapid downstream tool development and analysis by removing the burden of implementing these features in independent applications. We demonstrate the use of the SDK in an associated analysis notebook to evaluate 59,437 tumors from patients cataloged by the American Association for Cancer Research Project GENIE cohort. CIViCpy is open-source, Massachusetts Institute of Technology (MIT) licensed, and readily available for installation on the Python Package Index (PyPi; pypi.org). CIViCpy documentation is available online at civicpy.org.

**METHODS**

We designed the CIViCpy Python SDK as a standalone package to retrieve the CIViC knowledgebase content and transform responses into Python objects with intuitive structures and interobject linkages. The resulting software is a toolkit to support numerous downstream operations, including exploratory analyses, variant annotation, and application development (Fig 1). Here, we describe the optimizations and design choices made to construct CIViCpy.

**CIViCpy Objects**

The primary data class in CIViCpy is the CivicRecord. This class provides the framework for all first-class entities in CIViC: Genes, Variants, Variant Groups, Evidence, and Assertions. First-class entities are delineated from other object classes in CIViC by the combination of persistent public identifiers, dedicated API end points for returning object details, and tracked provenance (Table 1). Provenance tracking records the history of all actions taken on the object as part of the CIViC curation cycle: object submission, revisions, and editor approval. We also create CivicRecord objects from CIViC Sources, Users, and Organizations, despite their lack of provenance tracking; CivicRecord objects only require that a CIViC class is identifiable and has supporting API end points. Documentation for each of the CivicRecord subclasses can be found online at http://bit.ly/civicrecord-types.

The CIViCpy CivicAttribute is a data class for representing composite data entities not captured by CivicRecord. This includes composite entities with nested or list attributes (eg, diseases, coordinates, or variant_aliases), as opposed to primitive, single-valued entities (eg, description, allele_registry_id, or evidence_direction). CivicAttribute inherits from CivicRecord but is not indexed and accordingly overrides many of the features of its parent class. Importantly, CivicAttribute is not cached (see Caching) except as a linked object to other (non-CivicAttribute) CivicRecord objects, and cannot be retrieved independently.

One of the strengths of the CivicRecord class is the ability to dynamically evaluate nested CivicRecord objects. A Variant, for instance, may have multiple associated Evidence records, each of which may have a source linked to multiple Evidence records describing other Variants. A CivicRecord will automatically link nested objects; consequently, one can chain through linked objects when analyzing CIViC records to efficiently get to values of interest, such as evaluating the Association for Molecular Pathology/ASCO/College of American Pathologists somatic variant classification for a CIViC Assertion (Fig 1, Object Inspection). Therefore, when evaluating evidence for a variant using CIViCpy, the associated Evidence
objects are returned rather than a list of evidence identifiers. Evidence, in turn, will link to other CivicRecord objects (eg, Assertion, Source), which can also be explored. An example of exploring Assertions linked to a Variant using CIViCpy is provided in the Data Supplement (see the CIViCpy Objects section).

Querying CIViC

CIViC is built on a segregated server/client architecture, where all functionality of the CIViC Web client is managed through RESTful API calls to the underlying Rails server. CIViCpy leverages this architectural design to post complex queries to the CIViC advanced search API end points. This enables high-throughput searches for records of interest, including full data set requests. CIViC full data sets include Evidence and Assertions in multiple states of the CIViC review cycle: those that have been editor-reviewed and approved (accepted), those that are pending review (submitted), and those that have been rejected for inclusion in CIViC. Because the CIViC full data set contains rejected and submitted Evidence items and Assertions that have not been approved by CIViC editors, these records may be inaccurate, in a partial state, or incongruent with the CIViC knowledge model.

CivicRecord objects may be retrieved by the corresponding get_all functions (eg, get_all_variants(), get_all_assertions()). These functions may optionally be passed a parameter for explicitly including only objects of a given status. For example, a user may request only evidence that has been accepted or submitted (and exclude any rejected evidence). Although these behaviors are readily reproducible by users without leveraging this feature (eg, through inspection of evidence.status), we expect most downstream workflows would desire to include only accepted and/or submitted evidence, and so we have provided this functionality as a convenience. An example of filtering evidence by status using CIViCpy is provided in the Data Supplement (see the Filtering Evidence section).

Caching

CIViCpy also is a standalone component for services intended to perform large-volume operations on the CIViC knowledgebase. A key design consideration, therefore, is the local caching of CIViC content for quick retrieval and...
local indexing operations. When loaded, each cached CivicRecord is assigned a unique key using the native Python hash function, which is recomputed on loading a stored cache from disk (by design, the hash seed changes with each Python session). This hash is computed on the CivicRecord type and id values, such that user-generated partial CivicRecords with these minimal values provide the same hash (and are treated as equivalent to) complete CivicRecords.

Each cache also maintains a timestamp of when the cache was last generated. This information is used when loading the cache from file to determine whether a fresh cache needs to be built or retrieved from a remote source. CIViCpy will expire a cache 7 days (or after user-configurable length of time) after it is initially built and will retrieve the newest (nightly) cache from the CIViC live server. The local cache can also be manually updated from the command line with the civicpy update utility.

**Variant Coordinate Search**

When loading all variants from CIViC, a sorted variant coordinate index is also constructed after cache generation to enable coordinate search and lookup strategies (Fig 2A). A similarly sorted list of CoordinateQuery objects represent variants to query, such as those observed in a patient’s tumor (Fig 2B). The index and CoordinateQuery objects are used by the search algorithm for high-throughput searches (Fig 2C). Importantly, the search algorithm supports the notion of variant ranges for CIViC records and queries, and provides several search modes to accommodate varying sensitivity and specificity tradeoffs (Fig 2D).

**Variant Exports**

CIViCpy enables the export of CIViC Variant records and their associated Evidence Items and Assertions into the VCF (Fig 1) by providing a VCFWriter class. After instantiating a VCFWriter object, a Variant record may be added to it for future output by calling the addrecord() function. The addrecord() function supports various variant types, depending on the curated coordinates available for a Variant. All Variants require the chromosome name and start position. For single-nucleotide variants and complex variants, the reference sequence and altered sequence information also must be available. By contrast, insertions require only variant sequence information and deletions require only reference sequence information. Variants that do not meet these minimum requirements will not be added and a warning message is emitted instead. Fusions and other variants with a second set of coordinates are currently not supported. To verify whether a Variant can be added to a VCFWriter object, the convenience method is_valid_for_vcf() can be called on a Variant object before calling addrecord(). More information about variant types that may lack reference and variant sequence information (eg, fusions) can be found at bit.ly/civic-coordinates. Those variants that cannot be exported into the VCF format are still retrievable as CIViCpy records. Once all desired variants are added to the VCFWriter object, writerecords() needs to be called to write the VCF file. An example of using CIViCpy to generate a CIViC VCF file is provided in the Data Supplement (see the Exporting to VCF section).

The variants added to the VCFWriter object are written to the VCF file, one VCF record for each Variant object. If two Variant objects share the same chromosome, start position, and reference allele(s), they will not be combined into one VCF record but instead will be written as separate VCF records. Additional CIViC data are added to the VCF as annotations to the CSQ (consequence) INFO field (Table 2). CIViC Evidence items and Assertions linked to the Variant

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**TABLE 1. CIViC Class Entities**

| Civic Object     | Provenance Tracking | Persistent CIViC ID | Detailed Record End Point | CIViCpy Class |
|------------------|---------------------|---------------------|---------------------------|---------------|
| First-class entities |                     |                     |                           |               |
| Genes            | Y                   | Y                   | Y                         | CivicRecord   |
| Variants         | Y                   | Y                   | Y                         | CivicRecord   |
| Variant groups   | Y                   | Y                   | Y                         | CivicRecord   |
| Evidence         | Y                   | Y                   | Y                         | CivicRecord   |
| Assertions       | Y                   | Y                   | Y                         | CivicRecord   |
| Second-class entities |                 |                     |                           |               |
| User             | N                   | Y                   | Y                         | CivicRecord   |
| Organization     | N                   | Y                   | Y                         | CivicRecord   |
| Sources          | N                   | N                   | N                         | CivicRecord   |
| Country          | N                   |         | N                         | CivicAttribute|
| Drugs            | N                   | N                   | N                         | CivicAttribute|
| Diseases         | N                   | N                   | N                         | CivicAttribute|
| Phenotypes       | N                   | N                   | N                         | CivicAttribute|

Abbreviations: CIViC, Clinical Interpretations for Variants in Cancer; ID, identifier.
FIG 2. Variant coordinate search with CIVCpy. (A) On updating or loading the in-memory cache, all variant records are extracted and converted into a sorted Variant Coordinate Index (VCI). Variants missing coordinate values are excluded, and variants with compound coordinates (e.g., fusion variants) have the coordinates split into distinct records. Each coordinate is sorted by chromosome, start coordinate, stop coordinate, and alternate sequence (see the purple box). The VCI also contains a reference to the cache key for the corresponding variant. The vci_ptr serves an analogous role to the vci_ptr for the variant queries. (B) CoordinateQuery objects are used to query against the VCI and should match the coordinate system requirements from CIVIC. These objects contain an optional key field for user reference. When searching the knowledgebase for several variants, CoordinateQuery objects should be presorted by the same procedure for sorting the VCI. The q_ptr serves an analogous role to the vci_ptr for the variant queries. (C) Starting at the first sorted VCI and Query record, searches will increment the smaller of the vci_ptr or q_ptr until an overlapping coordinate range is identified. When overlaps occur, matches are reported on the basis of the search model specified. The vci_ptr is restored once all overlapping records for a query are evaluated. (D) Several search models exist for this algorithm, including a highly sensitive Any search, a conservative Exact search, and two intermediate modes. Overlap scenarios and report behavior for each scenario are presented. ✓, a scenario is reported; ✗, a scenario is not reported. QE, query encompassing; RE, record encompassing.

| State 1: VCI | Q          | State 2: VCI | Q          | State 3: VCI | Q          | State 4: VCI | Q          | State 5: VCI | Q          | State 6: VCI | Q          |
|-------------|------------|-------------|------------|-------------|------------|-------------|------------|-------------|------------|-------------|------------|
| Record 1    | Query 1    | Record 1    | Query 1    | Record 1    | Query 1    | Record 1    | Query 1    | Record 1    | Query 1    | Record 1    | Query 1    |
| Record 2    | Query 2    | Record 2    | Query 2    | Record 2    | Query 2    | Record 2    | Query 2    | Record 2    | Query 2    | Record 2    | Query 2    |
| Record 3    | Query 3    | Record 3    | Query 3    | Record 3    | Query 3    | Record 3    | Query 3    | Record 3    | Query 3    | Record 3    | Query 3    |
| Record 4    | Query 4    | Record 4    | Query 4    | Record 4    | Query 4    | Record 4    | Query 4    | Record 4    | Query 4    | Record 4    | Query 4    |
| tmp         |            |             | tmp        |             |             | tmp         |            |             |             |             |            |

| Comparison Values: | Record 1 > Query 1 | Actions: Increment q_ptr | Record 1 > Query 2 | Actions: Increment vci_ptr | Record 4 > Query 2 | Actions: Increment q_ptr | Record 4 > Query 2 | Actions: Increment vci_ptr |
|-------------------|-------------------|-------------------------|-------------------|-------------------------|-------------------|-------------------------|-------------------|-------------------------|
|                   | Record 1 > Query 1 | Actions: Increment q_ptr |                   | Record 2 > Query 2 | Actions: Increment vci_ptr |                   | Record 4 > Query 2 | Actions: Increment q_ptr |

For import into Google BigQuery (git.io/bigquery-variant-annotation).

A command line utility, civicpy create-vcf, allows users to create a VCF file of all supported CIVIC variants. The -v include-status required parameter will restrict the annotations to only those Evidence Items and Assertions that
match the given status(es). If a variant does not have any supporting Evidence Items or Assertions with the required statuses, it will not be included in the VCF.

**Software Engineering and Availability**  
The CIViCpy codebase is hosted publicly on GitHub (git.io/civicpy). The test suite is implemented using the pytest framework and GitHub integration tests are run using travis-ci (travis-ci.org). Coveralls (https://coveralls.io/) is used to track test coverage (77%). Code changes are integrated using GitHub pull requests (https://github.com/griffithlab/civicpy/pulls). Feature additions, user requests, and bug reports are managed using GitHub issue tracking (https://github.com/griffithlab/civicpy/issues). Collectively, these features enable robust community development and facilitate adoption of the CIViCpy SDK.

User documentation is written using reStructuredText markup language and the Sphinx documentation framework (sphinx-doc.org). Documentation is hosted on Read the Docs (readthedocs.org) and can be viewed at civicpy.org. This documentation serves as both a “quick start” guide and a detailed reference for developers and bioinformaticians.

This project is licensed under the MIT License (https://opensource.org/licenses/MIT). CIViCpy has been packaged and uploaded to the PyPI under the civicpy package name and can be installed by running the pip install civicpy command. Installation requires a Python version 3.7 environment. Releases are also made available on GitHub (https://github.com/griffithlab/civicpy/releases).

**GENIE Analysis**  
To evaluate the performance of CIViCpy in annotating patient data, we performed a demonstrative analysis in a Jupyter Notebook, available on the CIViCpy GitHub repository (git.io/civicpy-genie). The Project GENIE10 version 5.0 extended mutations file, which describes 445,655 variants across 59,437 patient tumors, was downloaded from https://www.synapse.org/#!Synapse:syn17394041. Coordinates from the reported variants were extracted and each coordinate set was tagged using the corresponding tumor sample barcode.

### TABLE 2: Variant Call Format CSQ Field Attributes

| CSQ Field         | Description                                                                 | Compound Field |
|-------------------|-----------------------------------------------------------------------------|----------------|
| Allele            | Alternate allele                                                            | Y              |
| Consequence       | CIViC sequence ontology variant types for this variant                      |                |
| SYMBOL            | HGNC gene symbol for the gene associated with this variant                  |                |
| Entrez Gene ID    | Entrez gene ID for the gene associated with this variant                    |                |
| Feature_type      | “transcript”                                                                 |                |
| Feature           | The Ensembl ID for the CIViC representative transcripts of this variant     |                |
| HGVSc             | Variant representation using HGVS notation (DNA level), corresponding to the Feature |                |
| HGVSp             | Variant representation using HGVS notation (protein level), corresponding to the Feature |                |
| CIViC Variant Name| The CIViC variant name of this variant                                       |                |
| CIViC Variant ID  | The CIViC internal ID for this variant                                       |                |
| CIViC Variant Aliases | CIViC aliases for this variant                                             |                |
| CIViC HGVS        | CIViC HGVS strings for this variant                                         |                |
| Allele Registry ID| The allele registry ID for this variant                                      |                |
| ClinVar IDs       | ClinVar IDs associated with this variant                                     |                |
| CIViC Variant Evidence Score| The CIViC evidence score for this variant                       |                |
| CIViC Entity Type | The type of entity being annotated, either “evidence” or “assertion”       |                |
| CIViC Entity ID   | The CIViC internal ID for the entity being annotated                        |                |
| CIViC Entity URL  | The CIViC direct URL to the entity being annotated                          |                |
| CIViC Entity Source| For evidence entities, the ID of the publication used to create the evidence including the source type in the format “sourceId_(sourceType)” | |
| CIViC Entity Variant Origin| The variant origin of the entity being annotated, either “Somatic,” “Rare Germline,” “Common Germline,” “Unknown,” or “N/A” | |
| CIViC Entity Status| The status of the CIViC entity being annotated, either “submitted,” “accepted,” or “rejected” | |

Abbreviations: CIViC, Clinical interpretation of Variants in Cancer; CSQ, consequence; HGNC, HUGO Gene Nomenclature Committee; HGVS, Human Genome Variation Society; ID, identifier; N/A, not applicable.

*Compound fields contain multiple values and use the ampersand (&) character to delineate values.
The extracted coordinates were then transformed into a sorted list of CIViCpy CoordinateQuery objects, which were passed to the bulk-query search method using an exact search strategy (Fig 2D). Match results and query times were recorded for the full set of GENIE variants in addition to timings from exponentially increasing subsets from one to 300,000. Match results from an anticonservative search strategy, which allowed for any coordinate overlap (Fig 2D), were also recorded.

Match results from the full set of variants were grouped by tumor identifier and summarized by counts of Exact, Any, and no matches. In addition, tumors for which no variations were reported for querying were also summarized. Finally, we grouped tumors on the number of variants matching CIViC evidence by Exact search, and summarized the highest level of evidence found across the tumors in those groups.

RESULTS

GENIE Tumor Variant Results

Using the Exact search strategy, CIViCpy successfully matched CIViC evidence to 7.6% (n = 34,642) of GENIE variants, and using the Any strategy, an additional 42.9% of variants (n = 195,349) were matched (Fig 3A). Furthermore, 46.3% of tumors (n = 27,545) had at least one Exact match to a reported variant and an additional 40.2% of tumors (n = 23,925) had at least one Any match. Notably, 8.7% of tumors (n = 5,200) in the cohort had no reported variants to query against the knowledgebase. We evaluated the highest CIViC evidence level reported for the 27,545 tumors with matched evidence, and found 14.0% of those tumors (n = 3,852) matched to a CIViC Validated Association (Level A). An additional 69.3% of tumors (n = 19,098) matched to Clinical Evidence (Level B). Fewer tumors had Case Study (Level C, 11.8%; n = 3,248), Preclinical (Level D, 3.9%; n = 1,066), or Inferential (Level E, 1.0%; n = 281) as the highest-level evidence match (Fig 3B). In total, 38.6% (n = 22,950) of all GENIE tumors (including those without reported variants) had at least one variant that matched to Level A or B evidence.

Tumors from the cohort had an average of 6.88 (median, 4) variants reported, and although most tumors (53.7%; n = 31,892) did not Exact match to CIViC variants, many tumors matched one (35.4%; n = 21,026), two (9.4%; n = 5,592), three (1.3%; n = 796), or more (0.2%; n = 131) CIViC variants.

FIG 3. Variant coordinate search with CIViCpy. (A) Querying GENIE variants against the CIViC knowledgebase results in 7.6% (n = 34,642) of variant (n = 445,655) and 46.3% (n = 27,545) of tumors (n = 59,437) with Exact matches to CIViC variants. Allowing for Any matches, these values increase to 50.5% of variants (n = 229,991) and 86.6% of tumors (n = 51,470). A small percentage (8.7%; n = 5,200) of all tumors had no reported variants with which to search. (B) Tumors were grouped by the number of variants that Exact matched CIViC records. For each tumor, the highest level of evidence supporting the matched variants was counted. We observed that 83.3% of tumors (n = 22,950) with Exact matching variants (which equates to 38.6% of all tumors) were linked to CIViC Validated (Level A) or Clinical (Level B) evidence. (C) Response time of CIViCpy bulk queries against the CIViC knowledgebase. As the number of variants queried increase > 1,000, response time is linear to the number of queries, with an increase in overall time of 0.808 ms/variant. CIViC, Clinical Interpretations for Variants in Cancer.
CIViCpy Search Performance

CIViCpy uses a search strategy (Fig 2C) designed to scale linearly with input query size. We evaluated the performance of CIViCpy annotation of the GENIE cohort and found that queries with \( \geq 1,000 \) variants scale linearly with input size, increasing total search time by approximately 0.808 ms/variant (Fig 3C). Queries with < 1,000 variants exhibit higher performance and are returned in < 1 second. We annotated the entire GENIE data set \((n = 445,655\) variants) in 369 seconds at a rate of 1,236 variants/s.

**DISCUSSION**

CIViCpy is an SDK and high-throughput analysis toolkit for exploring and analyzing content within the CIVIC knowledgebase. CIViCpy has tools for object inspection, with convenient features for record retrieval and search. Variant annotation through CIViCpy is demonstrated to handle variant searches at 1,236 variants/s through the provided coordinate search methods. In addition, the SDK provides convenient tools for exporting CIVIC content to VCF for integration in external annotation pipelines and tools.

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A.H.W. and S.K. contributed equally to this work. O.L.G. and M.G. contributed equally to this work.

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