Video Article

A Metadata Extraction Approach for Clinical Case Reports to Enable Advanced Understanding of Biomedical Concepts

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URL: https://www.jove.com/video/58392
DOI: doi:10.3791/58392

Keywords: This Month in JoVE, Issue 139, data science, medical informatics, text mining, annotation, curation, clinical case reports

Date Published: 9/20/2018

Citation: Caufield, J.H., Liem, D.A., Garlid, A.O., Zhou, Y., Watson, K., Bui, A.A., Wang, W., Ping, P. A Metadata Extraction Approach for Clinical Case Reports to Enable Advanced Understanding of Biomedical Concepts. *J. Vis. Exp.* (139), e58392, doi:10.3791/58392 (2018).

Abstract

Clinical case reports (CCRs) are a valuable means of sharing observations and insights in medicine. The form of these documents varies, and their content includes descriptions of numerous, novel disease presentations and treatments. Thus far, the text data within CCRs is largely unstructured, requiring significant human and computational effort to render these data useful for in-depth analysis. In this protocol, we describe methods for identifying metadata corresponding to specific biomedical concepts frequently observed within CCRs. We provide a metadata template as a guide for document annotation, recognizing that imposing structure on CCRs may be pursued by combinations of manual and automated effort. The approach presented here is appropriate for organization of concept-related text from a large literature corpus (*e.g.,* thousands of CCRs) but may be easily adapted to facilitate more focused tasks or small sets of reports. The resulting structured text data includes sufficient semantic context to support a variety of subsequent text analysis workflows: meta-analyses to determine how to maximize CCR detail, epidemiological studies of rare diseases, and the development of models of medical language may all be made more realizable and manageable through the use of structured text data.

Video Link

The video component of this article can be found at https://www.jove.com/video/58392/

Introduction

Clinical case reports (CCRs) are a fundamental means of sharing observations and insights in medicine. These serve as a basic mechanism of communication and education for clinicians and medical students. Historically, CCRs have also provided accounts of emerging diseases, their treatments, and their genetic backgrounds[1,2,3,4]. For example, the first treatment of human rabies by Louis Pasteur in 1885[5,6] and the first application of penicillin in patients[7] were both reported through CCRs. More than 1.87 million CCRs have been published as of April 2018, with over half a million within the last decade; journals are continuing to provide new venues for these reports[8]. Though unique in form and content, CCRs contain text data that are largely unstructured, contain a vast vocabulary, and concern interrelated phenomena, limiting their use as a structured resource. Significant effort is required to extract detailed metadata (*i.e.,* "data about data", or in this case, descriptions of document contents) from CCRs and establish them as a findable, accessible, interoperable, and reusable (FAIR)[9] data resource.

Here, we describe a process for extracting text and numerical values to standardize the description of specific biomedical concepts within published CCRs. This methodology includes a metadata template to guide annotation; see **Figure 1** for an overview of this process. Application of the annotation process to a large collection of reports (*e.g.,* several thousand of a specific type of disease presentation) permits assembly of a manageable and structured set of annotated clinical texts, achieving machine-readable documentation and biomedical phenomena embedded within each clinical presentation. Though data formats such as those provided by HL7 (*e.g.*, Version 3 of the Messaging Standard[10] or the Fast Healthcare Interoperability Resources [FHIR][11]), LOINC[12], and revision 10 of the International Statistical Classification of Diseases and Related Health Problems (ICD-10)[13] provide standards for describing and exchanging clinical observations, they do not capture the text surrounding these data, nor are they intended to. The results of our methodology are best used to enforce structure on CCRs and facilitate subsequent

analysis, normalization through controlled vocabularies and coding systems (*e.g.*, ICD-10), and/or conversion to the clinical data formats listed above.

Mining CCRs is an active area of work within biomedical and clinical informatics. Though previous proposals to standardize the structure of case reports (*e.g.*, using HL7 v2.5[14] or standardized phenotype terminology[15]) are commendable, it is likely that CCRs will continue to follow a variety of different natural-language forms and document layouts, as they have for much of the past century. Under ideal conditions, authors of new case reports follow CARE guidelines[16] to ensure they are comprehensive. Approaches sensitive to both natural language and its relation to medical concepts may therefore be most effective in working with new and archived reports. Resources such as CRAFT[17] and those produced by Informatics for Integrating Biology and the Bedside (i2b2)[18] curation support natural language processing (NLP) approaches yet do not specifically focus on CCRs or clinical narratives. Similarly, medical NLP tools such as cTAKES[19] and CLAMP[20] have been developed but generally identify specific words or phrases (*i.e.*, entities) within documents rather than the general concepts commonly described in CCRs.

We have designed a standardized metadata template for features commonly included within CCRs. This template defines features to impose structure on CCRs—an essential precursor for in-depth comparisons of document contents-yet allows for sufficient flexibility to retain semantic context. Though we have designed the format associated with this template to be appropriate for both manual annotation and computationally-assisted text mining, we have ensured it is particularly easy to use for manual annotators. Our approach noticeably differs from more intricate (and, therefore, less immediately understandable to untrained researchers) frameworks such as FHIR[21]. The following protocol describes how to isolate document features corresponding to each template data type, with a single set of values corresponding to those in a single CCR.

The data types within the template are those most descriptive for CCRs and patient-focused medical documents in general. Annotation of these features promotes findability, accessibility, interoperability, and reusability of CCR text, primarily by giving it structure. The data types are in four general categories: document and annotation identification, case report identification (*i.e.,* document-level properties), medical content concepts (primarily concept-level properties), and acknowledgements (*i.e.,* features providing evidence of funding). In this annotation process, each document includes the full text of a CCR, omitting any document contents material independent to the case (*e.g.,* experimental protocols). CCRs are generally less than 1,000 words each; a single corpus should ideally be indexed by the same bibliographic database and be in the same written language.

The product of the approach described here, when applied to a CCR corpus, is a structured set of annotated clinical text. While this methodology can be performed fully manually and has been designed to be performed by domain experts without any informatics experience, it complements the natural language processing approaches specified above and provides data appropriate for computational analysis. Such analyses may be of interest to audiences of researchers beyond those who frequently read CCRs, including:

- those concerned with disease presentations, their key symptomology, usual diagnostic approaches, and treatments
- those who wish to compare the results of clinical trials with events described within the clinical literature, potentially providing additional observations and greater statistical power.
- bioinformatics, biomedical informatics, and computer science researchers who require structured medical language data sets or high-level understandings of medical narratives
- Government policy researchers focusing on how clinical trials may best reflect how diagnosis and treatment as it occurs in reality

Enforcing structure on CCRs can support numerous subsequent efforts to better understand both medical language and biomedical phenomena.

Protocol

1. Document and Annotation Identification

Note: Values in this category support the annotation process.

1. Using the annotation template, provide an identifier specific to this metadata set, *e.g.*, ***Case123***. The identifier format should be consistent throughout the project (*e.g.,* ***Case001*** through ***Case500***).
2. Specify the date on which a document was read and annotated. Use a format resembling “Jan 10 2018” for consistency and readability.

2. Case Report Identification

Note: Values in this category provide document-level features and contribute to a document’s findability.

1. Be consistent with the format of each field across all annotations, *e.g.,* individual values should be separated by semicolons without following spaces in all entries. Use identical formats to those used in the original document *or* those used in a bibliographic database such as MEDLINE.
2. Provide the title of the document.
3. Provide the names of all authors of the document in the provided order. Normalize the format of all names, such that all names take the form of a single last name followed by any number of initials, *e.g.* Jane B. Park becomes ***Park JB***. Do not include titles. Separate multiple authors with a semicolon without additional punctuation, such that John A. Smith, Jane B. Park takes a form of **Smith JA;Park JB.**
4. Provide the year of publication of the document.
5. Provide the full title of the journal in which the document was published. A list of controlled journal names is provided by the NLM Catalog (https://www.ncbi.nlm.nih.gov/nlmcatalog)**.**
6. Provide the address of the home institution of the authors of the document, as specified in the document. This may include departments, geographic locations, and postal address details.

1. If multiple locations are provided (*e.g.,* if affiliations differ between authors), specify only details for the corresponding author. If a corresponding author cannot be identified, use that of the first author, or do not specify an institution. If a corresponding author has multiple affiliations, specify both and separate with a semicolon.

7. Provide the corresponding author of the document, as specified within the document heading using the same format as that used in the Authors data type.
8. Provide a document identifier (*e.g.,* a PMID).
9. Provide a Digital Object Identifier, where possible and available, resolvable to the document URL (through https://www.doi.org/), not a PubMed Central page.
10. Provide a stable URL to the full text of the document, if available**.** To maximize accessibility, this may refer to the PubMed Central version.
11. Provide the document language. For documents available in multiple languages, provide both, separated with a semicolon.

3. Medical Content

Note: Values in this category identify document-level, concept-level, and text-level features. They serve to enhance a document's accessibility, interoperability, and reusability. These features provide ways to observe conceptual and semantic similarities between document content, with a focus on biomedical topics and events. Most categories in this section can include multiple text statements and each should be separated using a semicolon.

1. Include contextual detail in each field (*e.g.,* "mother had breast cancer at age 50") rather than providing only terms from a controlled vocabulary (*e.g.,* not "breast cancer" alone). Do not include extensive detail beyond each observation.
2. Omit commonly repeated words and phrases (*e.g.,* pronouns, the word "patient", and the phrases "complained of" or "presented with"). Though subjectivity across multiple annotators is likely, it may be reduced by having multiple annotators for each document and through automated normalization after data collection. Computational post-processing approaches will vary by subsequent analysis needs and are not discussed here in detail.
3. Provide the following information in the annotation template.
    1. Provide specific terms identified within a document, usually in its header, as key terms. Separate with a semicolon as terms may include other punctuation.
    2. Provide demographic values, specifically any text statements describing a patient's background, including sex and/or gender, age, ethnicity, or nationality.
    3. Provide geographic locations mentioned within the clinical narrative, other than specific institution addresses. This should not include anatomical locations/parts, but may include any geographic locale where the patient resides or travels.
    4. Provide life style values, including any text statements describing frequent patient activities or behaviors relevant to their general health. In practice, this frequently involves smoking or alcohol consumption habits, but may also include sun exposure, diet, or frequency of specific types of physical activity.
    5. Provide medical history values referring to family history. Include any text statements describing clinical observations of and events experienced by siblings, parents, and other family members. This includes genetic conditions and negative observations (*i.e.,* ***family history was negative for*** a disease)**.**
    6. Provide values referring to Social History, including any text statements describing patient background not covered in Demography or Life Style. There may be overlaps in content between these categories. The statements may include occupational history and social habits.
    7. Provide values referring to the patient's medical and surgical history. Include any text statements describing any medical observations, treatments, or other events taking place prior to the beginning of the clinical presentation. This includes obstetric history and periods of good health, where noted.
    8. Specify one or more of the following 16 disease system categories. Note that these values are categorical rather than free-text. Categories are not comprehensive but should indicate most systems impacted by the events described in the clinical presentation and diagnosed disease.
        1. Follow a specific set of categories, based on the categories used in the International Statistical Classification of Diseases and Related Health Problems, revision 10 (ICD-10) code system. See **Table 1** for the list of disease system categories along with corresponding ICD-10 code ranges.

    9. Provide details of all signs and symptoms**.** Include any text statements describing any medical observations of signs or symptoms beginning at initial presentation, including their onset, duration, severity, and resolution, if provided. Do not include symptoms described in the outcome. These values may overlap with other types if symptoms continue from history to initial presentation.
    10. Provide details of any comorbidities. Include any terms or phrases describing distinct diseases present at the time of initial clinical presentation. There is likely overlap between these values and those in clinical history, though Comorbidity should not include terms identical to those in the Diagnosis.
    11. Provide details of all diagnostic techniques and procedures. Include the names of medical procedures done for diagnostic purposes, including examinations, tests, and imaging, as well as the conditions under which these tests were performed and relevant anatomical locations (*e.g.,* "upper extremity venous ultrasound"). Exclude test results.
    12. Provide details of diagnosis. Include any text statements describing diagnoses of disease, even if the final diagnosis is ambiguous.
    13. Provide all laboratory values and test results. Include names of diagnostic tests, their values, and conditions under which they were performed. This will involve overlap with terms used in the Diagnostic Techniques and Procedures data type. Both numerical and qualitative values (*e.g.,* ***complete blood count was within normal limits***) are acceptable**.** If the names of diagnostic tests are not provided, use terms describing the results (*e.g.,* ***leukopenia***), though they should also be included in the Signs and Symptoms.
    14. Provide details of pathology. Include any text statements describing results of pathology and histology studies, including gross pathology, immunology, and microscopy studies. Terms may overlap with those used in Diagnostic Techniques and Procedures (step 3.11), *e.g.,* with the procedures performed to obtain samples such as biopsy.

15. Provide all pharmacological therapies. Include any text statements describing drug therapies used in the course of treatment, including general terms such as ***antibiotics*** or specific drug names**.** Also, include descriptions of when and how drug therapies were stopped.
16. Provide all interventional procedures. Include any text statements describing therapeutic procedures used in the course of treatment, including invasive procedures, implantation of medical devices, and procedures done to facilitate other therapies. Also, include descriptions of when and how ongoing therapeutic procedures were stopped, if necessary.
17. Provide the patient outcome. Include any text statements describing health of the patient as of the end of the clinical presentation described in the report, including any follow-up tests.
18. Provide counts of all diagnostic images, figures, videos/animations, and tables. Include all counts of visual media included in the report, in the following format: Count of images; Count of figures; Count of videos or animations; Count of tables.
    1. Distinguish between images and figures in this way: images include any products of clinical diagnostics, including photographs, micrographs, electrocardiogram rhythm images, and other products of diagnostic imaging, while figures are all other images, generally including data plots and illustrations.
19. Provide evidence of relationships to other CCRs. This field may include identifiers (*e.g.,* PMIDs) of other reports in the data set cited by or referencing this report.
20. Provide evidence of relationships to clinical trials. This field may include identifiers of clinical trials citing this CCR. Identify trials by their ClinicalTrials.gov identifiers, preceded by NCT, or other stable identifier.
21. Include database crosslinks corresponding to this document, including identifiers, preferably as database names and stable URLs.

4. Acknowledgements

Notes: Values in this category identify document-level features yet have little consistent structure across publications. They provide details regarding the organizations providing support for a CCR and related work. This category also includes a field for the total count of references cited by an article: this is intended to provide a rough metric of the degree to which a document has conceptual relationships with other biomedical documents of any type. Within the four data types in this section, provide the following.

1. Specify all funding sources supporting the work and corresponding PI as well as relevant award numbers. The first value, Funding Source, should include the names of all organizations providing financial support for the work.
    1. Separate organizations with semicolons and spaces, *e.g.*, ***National Institutes of Health/National Cancer Institute***; ***DOE***; ***Smith-Park Foundation***.
    2. For the following value, Award Number, specify any award numbers or specific designations provided along with the recipients of the awards, where appropriate, as initials of the recipients in parentheses, *e.g.*, ***R01HL123123 (to JP)***, ***NS12312 (to JP, JS)***, ***research training fellowship (to JS)***. Authors may explicitly state that no corresponding information is available (*e.g.,* "no funding was received"); in these cases, use the text provided by the authors as the Funding Source value. Otherwise, the value should be NA.
2. Specify disclosures/conflicts of interest as specified by the authors, *e.g.*, ***JP is a consultant for DrugCo***. Authors may explicitly state that no corresponding information is available (*e.g.,* "no conflict of interest is declared"); in these cases, use the text provided by the authors as the Disclosures/Conflict of Interest value. Otherwise, as above, the value should be NA.
3. Specify a numerical count of all references cited by the document, not including those provided in any supplementary material. No reference text should be included in this field.

Representative Results

An example of the annotation process is shown in **Figure 2**. This case[22] describes a presentation of infection by the bacterial pathogen *Burkholderia thailandensis*. For reference, the relevant portion of this CCR is provided in plain text format in **Supplementary File 1**; some research findings are also presented in this report and are included for comparison. In practice, converting reports provided in HTML or PDF format to plain text may improve the efficiency and ease of metadata extraction.

Examples of two sets of completed CCR metadata annotations are provided in **Table 2**. The first of these examples is mock data to illustrate the ideal format of each value, while the second example contains values extracted from a published CCR on a rare condition, acrodermatitis enteropathica[23].

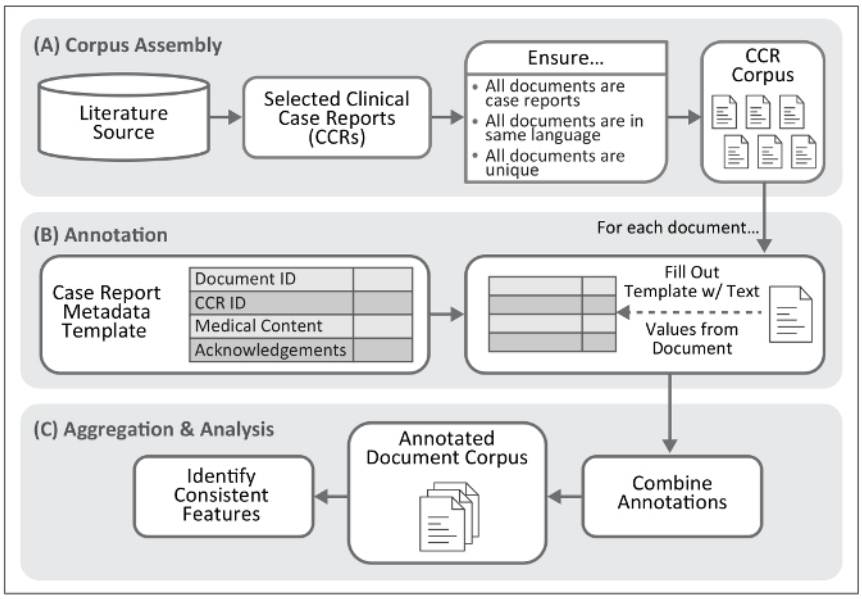
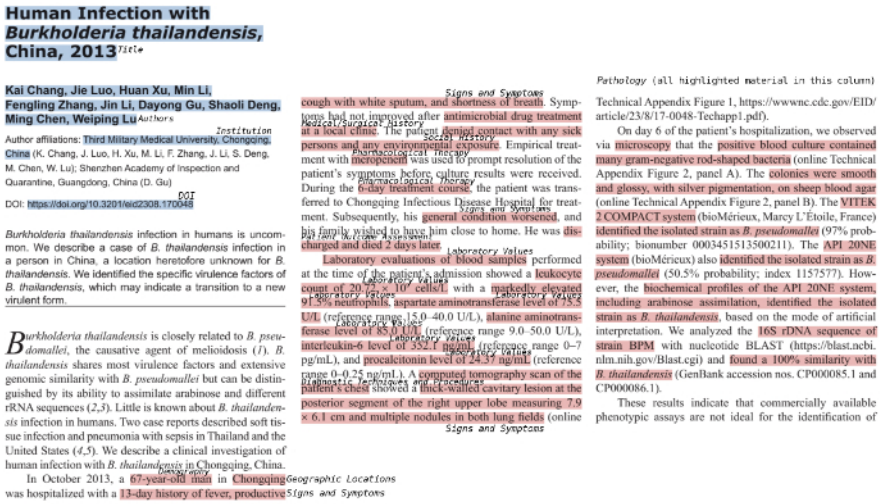


Figure 1. Workflow for Case Report Annotation. The protocol described here provides a method for identification of textual features frequently present within clinical case reports. This process requires assembly of a document corpus. The product of the annotation process, once aggregated into a single file, permits identification of text features associated with medical concepts and their descriptions within case reports. Please click here to view a larger version of this figure.



Human Infection with *Burkholderia thailandensis*, China, 2013

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DOI: https://doi.org/10.3201/eid2308.170046

Burkholderia thailandensis infection in humans is uncommon. We describe a case of *B. thailandensis* infection in a person in China, a location heretofore unknown for *B. thailandensis*. We identified the specific virulence factors of *B. thailandensis*, which may indicate a transition to a new virulent form.

Burkholderia thailandensis is closely related to *B. pseudomallei*, the causative agent of melioidosis (*1*). *B. thailandensis* shares most virulence factors and extensive genomic similarity with *B. pseudomallei* but can be distinguished by its ability to assimilate arabinose and different rRNA sequences (*2*,*3*). Little is known about *B. thailandensis* infection in humans. Two case reports described soft tissue infection and pneumonia with sepsis in Thailand and the United States (*4*,*5*). We describe a clinical investigation of human infection with *B. thailandensis* in Chongqing, China.

In October 2013, a 67-year-old man in Chongqing was hospitalized with a 13-day history of fever, productive cough with white sputum, and shortness of breath. Symptoms had not improved after antimicrobial drug treatment at a local clinic. The patient denied contact with any sick persons and any environmental exposure. Empirical treatment with meropenem was used to prompt resolution of the patient's symptoms before culture results were received. During the 6-day treatment course, the patient was transferred to Chongqing Infectious Disease Hospital for treatment. Subsequently, his general condition worsened, and his family wished to have him close to home. He was discharged and died 2 days later.

Laboratory evaluations of blood samples performed at the time of the patient's admission showed a leukocyte count of 20.72 × 10⁹ cells/L with a markedly elevated 97.5% neutrophils, aspartate aminotransferase level of 73.5 U/L (reference range 15.0–40.0 U/L), alanine aminotransferase level of 85.0 U/L (reference range 9.0–50.0 U/L), interleukin-6 level of 352.1 ng/mL (reference range 0–7 pg/mL), and procalcitonin level of 24.37 ng/mL (reference range 0–0.25 ng/mL). A computed tomography scan of the patient's chest showed a thick-walled cavitary lesion at the posterior segment of the right upper lobe measuring 7.9 × 6.1 cm and multiple nodules in both lung fields (online Technical Appendix Figure 1, https://wwwnc.cdc.gov/EID/article/23/8/17-0048-Techapp1.pdf).

On day 6 of the patient's hospitalization, we observed via microscopy that the positive blood culture contained many gram-negative rod-shaped bacteria (online Technical Appendix Figure 2, panel A). The colonies were smooth and glossy, with silver pigmentation, on sheep blood agar (online Technical Appendix Figure 2, panel B). The VITEK 2 COMPACT system (bioMérieux, Marcy L'Étoile, France) identified the isolated strain as *B. pseudomallei* (97% probability; bionumber 0003451513500211). The API 20NE system (bioMérieux) also identified the isolated strain as *B. pseudomallei* (50.5% probability; index 1157577). However, the biochemical profiles of the API 20NE system, including arabinose assimilation, identified the isolated strain as *B. thailandensis*, based on the mode of artificial interpretation. We analyzed the 16S rDNA sequence of strain BPM with nucleotide BLAST (https://blast.ncbi.nlm.nih.gov/Blast.cgi) and found a 100% similarity with *B. thailandensis* (GenBank accession nos. CP000085.1 and CP000086.1).

These results indicate that commercially available phenotypic assays are not ideal for the identification of

Figure 2. Identification of Concept-Specific Text in a Clinical Case Report. Beginning with the text of a case report, a manual annotator may progress through the document, identifying segments of text corresponding to each component of the metadata template. Identification features are highlighted in blue. Text corresponding to medical concepts are in red and labeled with their type; all highlighted text in the third column refers to the Pathology type. Please click here to view a larger version of this figure.

Category	Description	ICD-10 Chapter	ICD-10 Code Range
cancer	Any type of cancer or malignant neoplasm.	II	C00-D49
nervous	Any disease of the brain, spine, or nerves.	VI	G00-G99
cardiovascular	Any disease of the heart or vascular system. Does not include hematological diseases.	IX	I00-I99
musculoskeletal and rheumatic	Any disease of the muscles, skeletal system, joints, and connective tissues.	XIII	M00-M99
digestive	Any disease of the gastrointestinal tract and digestive organs, including the liver and pancreas.	XI	K00-K95
obstetrical and gynecological	Any disease relating to pregnancy, childbirth, the female reproductive system, or the breasts.	XIV; XV	O00-O9A; N60-N98
infectious	Any disease causes by infectious microorganisms.	I	A00-B99
respiratory	Any disease of the lungs and respiratory tract.	X	J00-J99
hematologic	Any disease of the blood, bone marrow, lymph nodes, or spleen.	III	D50-D89
kidney and urologic	Any disease of the kidneys or bladder, including the ureters, as well as the male reproductive organs, including the prostate.	XIV	N00-N53; N99
endocrine	Any disease of the endocrine glands, as well as metabolic disorders.	IV	E00-E89
oral and maxillofacial	Any condition involving the mouth, jaws, head, face, or neck.	XI; XIII	K00-K14; M26-M27
eye	Any condition involving the eyes, including blindness.	VII	H00-H59
otorhinolaryngologic	Any condition of the ear, nose, and/or throat.	VIII	H60-H95; J30-J39
skin	Any disease of the skin.	XII	L00-L99
rare	A special category reserved for reports of rare diseases, defined as those impacting fewer than 200,000 individuals in the United States (see https://rarediseases.info.nih.gov/diseases)	*NA*	*NA*

Table 1. Disease Categories for Document Annotation. The categories listed here are those to be used for the Disease System data type in the document metadata template. As each disease presentation may involve multiple organ systems or etiologies, a single clinical case report may correspond to multiple categories. These categories largely follow those used to differentiate sections of the International Statistical Classification of Diseases and Related Health Problems, revision 10 (ICD-10) code system: corresponding ICD-10 chapters and code ranges are provided. Some categories, such as that for *oral and maxillofacial* disease, correspond to multiple sections of the ICD-10 system.

Data Type	Example #1	Example #2 (Cameron and McClain 1986)
Document and Annotation Identification		
Internal ID	CCR005	CCR2000
Annotation Date	Mar 2 2018	Mar 1 2018
Case Report Identification		
Title	A case of endocarditis.	Ocular histopathology of acrodermatitis enteropathica.
Authors	Grant AB;Chang CD	Cameron JD;McClain CJ
Year	2017	1986
Journal	World Journal of Medicine and Case Reports	British Journal of Ophthalmology
Institution	Department of Medicine, Division of Cardiology, First General Hospital, Boston, Massachusetts, USA	Department of Ophthalmology, University of Minnesota Medical School, Minneapolis, Minnesota 55455
Corresponding Author	Grant AB	Cameron JD
PMID	25555555	3756122
DOI	10.1011/wjmcr.2017.11.001	NA
Link	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC9555555/	https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1040795/
Language	English	English
Medical Content		
Key Words	brucellosis; endocarditis; mitral valve	NA
Demography	37-year-old male	male child
Geographic Locations	Florida; Rio de Janeiro, Brazil	NA
Life Style	smoker; drinks alcohol occasionally	NA
Family History	third of five children of consanguineous parents; younger brother has chronic eczema	NA
Social History	construction worker	NA
Medical/Surgical History	history of fatigue	8 pound 9 ounce (3884 g) product of an uncomplicated, full term pregnancy; in good health until age 1 month when he developed a blistering skin rash on his cheeks; rash spread to involve the skin around the eyes, nose, and mouth; skin lesions were also noted on the abdomen and extremities; diarrhoea and failure to thrive; skin biopsy at that time showed parakeratosis typical of acrodermatitis enteropathica; treated over the next six years with intermittent courses of broad spectrum antibiotics, breast milk, and diodoquin; partially responded; developed total alopecia, intermittent acrodermatitis, and intermittent diarrhoea with suboptimal weight gain; spasticity attributed to central nervous system involvement by the ae had developed by 8 months of age; several episodes of cardiopulmonary arrest at 11 months; lack of co-ordination of his vocal cords; tracheostomy; by age 18 months the child developed searching nystagmus associated with bilateral optic atrophy and slight attenuation of retinal vessels as well as signs of psychomotor retardation; bilateral keratoconjunctivitis; skin rash; second skin biopsy performed at age 3 again showed parakeratosis typical for ae; severe skin rash and diarrhoea; bilateral gross anterior corneal opacities were seen which had completely resolved by the time he was reexamined at age five; frequent infections

		including otitis media, urinary tract infections, and skin infections
Disease System	cardiovascular; infectious	digestive; skin; eye; rare
Signs and Symptoms	palpitations and dyspnea in the previous week; presented with lethargy, headache, and chills	severe blepharoconjunctivitis and bilateral anterior corneal vascularisation; severe skin rash and diarrhoea; gram-negative bacterial sepsis; skin lesions typical of acrodermatitis enteropathica, absence of thymic tissue, marked degeneration of the optic nerves, chiasm, and optic tracts and extensive cerebellar degeneration
Comorbidity	hypertension; hyperlipidemia	NA
Diagnostic Techniques and Procedures	Physical examination; electrocardiography; blood cultures	ocular examination; necropsy
Diagnosis	Brucella endocarditis	acrodermatitis enteropathica
Laboratory Values	increase in c-reactive protein (9 mg/dl); alkaline phosphatase (250 u/l)	NA
Pathology	Brucella melitensis was cultured from blood samples	right and left eyes were similar in appearance; corneal epithelium was reduced in thickness to one to three cell layers of flattened squamous epithelial cells over the entire surface of the cornea; all polarity of the epithelium was lost. bowman's membrane could be identified only in the periphery of the right cornea. no bowman's membrane could be identified in the left cornea. neither degenerative nor inflammatory pannus could be identified in either eye; extensive atrophy of the circular and oblique muscles of the ciliary body; some posterior migration of lens capsular epithelium and early cortical degenerative changes; extensive degeneration of the retinal pigment epithelium throughout the posterior pole; retina was attached and showed mild autolytic changes throughout; some preservation of rod and cone outer segments in the posterior pole, however, these structures were completely lost anterior to the equator; extensive loss of the ganglion cell and nerve fibre layers of both eyes; nearly complete atrophy of the disc and adjacent optic nerve
Pharmacological Therapy	gentamycin 240 mg/iv/daily	NA
Inverventional Therapy	prosthetic valve replacement	NA
Patient Outcome Assessment	recovery was uneventful; discharged home	died in 1971 (age 7)
Diagnostic Imaging/Videotape Recording	2;1;0;1	7;0;0;0
Relationship to Other Case Reports	5555555	23430849
Relationship with Clinial Trial	NCT05555123	NA
Crosslink with Database	MedlinePlus Health Information: https://medlineplus.gov/ency/article/000597.htm	HighWire - PDF: http://bjo.bmj.com/cgi/pmidlookup?view=long&pmid=3756122; Europe PubMed Central: http://europepmc.org/abstract/MED/3756122; Genetic Alliance: http://www.diseaseinfosearch.org/result/143
Acknowledgements		
Funding Source	National Institutes of Health/National Heart, Lung, and Blood Institute	The Minnesota Lions Club; Research to Prevent Blindness; Veterans Administration; Office of Alcohol and Other Drug Abuse Programming of the State of Minnesota
Award Number	R01HL123123 (to AG)	NA
Disclosures/Conflict of Interest	Dr. Grant is a paid spokesperson for DrugCo.	NA

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Table 2. Standardized Metadata Template for Clinical Case Reports, with Example Annotations. A set of features common to clinical case reports and facilitating their concept-level annotations is shown here. This template is arranged into three primary sections: Identification, Medical Content, and Acknowledgments, denoting the purpose and additional value afforded by each type of case report feature. This table contains two sets of example annotations, one of a fictionalized case report, and another set derived from a report on the condition acrodermatitis enteropathica[23].

Supplementary File 1. Text of a clinical case report (Chang *et al.* 2017). Please click here to download this file.

Discussion

Implementation of a standardized metadata template for CCRs can make their content more FAIR, expand their audience, and extend their applications. Following the traditional use of CCRs as educational tools in medical communications, healthcare trainees (*e.g.,* medical students, interns, and fellows), and biomedical researchers may find that summarized case report contents enable more rapid comprehension. The greatest strength of metadata standardization with CCRs, however, is that indexing these data transforms otherwise isolated observations into interpretable patterns. The protocol provided here can serve as the first step in a workflow for working with CCRs, whether this workflow consists of epidemiological analysis, post-marketing drug or treatment surveillance, or broader surveys of pathogenesis or therapeutic efficacy. Structured features identified within CCRs can provide a useful resource for researchers focusing on disease presentations and treatments, particularly for rare conditions. Clinical researchers may find data on past treatment regimens to analyze recorded symptoms or side effects and degree of improvement under previous standards of care. The data may also drive broader analyses of a new treatments based on efficacy, lack of adverse effects or toxicity, or on drug targeting differences in gender, age group, or genetic background.

The benefits provided by structured metadata are similarly applicable to computational workflows designed to parse or model medical language. Structured CCR features may also provide evidence of areas where report authors may provide more easily machine-readable (and in some cases, human-readable) content. Variance among CCRs can result from a lack of explicitly provided observations: *e.g.,* a patient's exact age may not be specified. Similarly, clinicians may not mention tests if the diagnostics or their results were considered trivial. By providing examples of gaps necessary for in-depth analysis, enforcing structure on CCRs highlights potential improvements. In a broader perspective, a greater availability of structured text data from medical documents supports natural language processing (NLP) efforts to learn from big data in healthcare[24,25].

Disclosures

The authors have nothing to disclose.

Acknowledgements

This work was supported in part by National Heart, Lung, and Blood Institute: R35 HL135772 (to P. Ping); National Institute of General Medical Sciences: U54 GM114833 (to P. Ping, K. Watson, and W. Wang); National Institute of Biomedical Imaging and Bioengineering: T32 EB016640 (to A. Bui); a gift from the Hoag Foundation and Dr. S. Setty; and the T.C. Laubisch endowment at UCLA (to P. Ping).

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