

UCSF

UC San Francisco Previously Published Works

Title

Identifying Symptom Information in Clinical Notes Using Natural Language Processing.

Permalink

<https://escholarship.org/uc/item/51n4p78v>

Journal

Nursing Research, 70(3)

ISSN

0029-6562

Authors

Koleck, Theresa A
Tatonetti, Nicholas P
Bakken, Suzanne
[et al.](#)

Publication Date

2021-05-01

DOI

10.1097/nnr.0000000000000488

Peer reviewed



Published in final edited form as:

Nurs Res. 2021 ; 70(3): 173–183. doi:10.1097/NNR.0000000000000488.

Identifying Symptom Information in Clinical Notes Using Natural Language Processing

Theresa A. Koleck, PhD, RN [Assistant Professor],

University of Pittsburgh School of Nursing, Pittsburgh, PA

Nicholas P. Tatonetti, PhD [Associate Professor],

Columbia University Department of Biomedical Informatics, Columbia University Department of Systems Biology, Columbia University Department of Medicine, Columbia University Institute for Genomic Medicine, Columbia University Data Science Institute, New York, NY

Suzanne Bakken, PhD, RN, FAAN, FACMI [Professor],

Columbia University School of Nursing, Columbia University Department of Biomedical Informatics, Columbia University Data Science Institute, New York, NY

Shazia Mitha, MPhil, MSN, AGACNP-BC, RN [PhD Candidate],

Columbia University School of Nursing, New York, NY

Morgan M. Henderson, BSN [Student],

University of Pittsburgh School of Nursing, Pittsburgh, PA

Maureen George, PhD, RN, AE-C, FAAN [Associate Professor],

Columbia University School of Nursing, New York, NY

Christine Miaskowski, PhD, RN, FAAN [Professor],

University of California, San Francisco School of Nursing, San Francisco, CA

Arlene Smaldone, PhD, CPNP-PC, CDE, FAAN [Professor],

Columbia University School of Nursing, Columbia University College of Dental Medicine, New York, NY

Corresponding author: Maxim Topaz, PhD, RN, Columbia University School of Nursing, 560 West 168th Street, New York, NY 10032, (mt3315@cumc.columbia.edu).

Theresa A. Koleck, PhD, RN, is Assistant Professor, University of Pittsburgh School of Nursing, Pittsburgh, PA. At the time this research was completed, she was an Associate Research Scientist, Columbia University School of Nursing, New York, NY.

Nicholas P. Tatonetti, PhD, is Associate Professor, Columbia University Department of Biomedical Informatics, Department of Systems Biology, Department of Medicine, Institute for Genomic Medicine, and Data Science Institute, New York, NY.

Suzanne Bakken, PhD, RN, FAAN, FACMI, is Professor, Columbia University School of Nursing, Department of Biomedical Informatics, and Data Science Institute, New York, NY.

Shazia Mitha, MS, AGACNP-BC, RN, is a PhD Candidate, Columbia University School of Nursing, New York, NY.

Morgan M. Henderson is a BSN Student, University of Pittsburgh School of Nursing, Pittsburgh, PA.

Maureen George, PhD, RN, AE-C, FAAN, is Associate Professor, Columbia University School of Nursing, New York, NY.

Christine Miaskowski, PhD, RN, FAAN, is Professor, University of California, San Francisco School of Nursing, San Francisco, CA.

Arlene Smaldone, PhD, CPNP-PC, CDE, FAAN, is Professor, Columbia University School of Nursing and College of Dental Medicine, New York, NY.

Maxim Topaz, PhD, RN, is Associate Professor, Columbia University School of Nursing and Data Science Institute, New York, NY.

The authors have no conflicts of interest to report.

Ethical Conduct of Research: This study was approved by the Columbia University Irving Medical Center Institutional Review Board.

Clinical Trial Registration: N/A

Maxim Topaz, PhD, RN [Associate Professor]

Columbia University School of Nursing, Columbia University Data Science Institute, New York, NY

Abstract

Background: Symptoms are a core concept of nursing interest. Large-scale secondary data reuse of notes in electronic health records (EHRs) has the potential to increase the quantity and quality of symptom research. However, the symptom language used in clinical notes is complex. A great need exists for methods designed specifically to identify and study symptom information from EHR notes.

Objectives: We aim to describe a method that combines standardized vocabularies, clinical expertise, and natural language processing (NLP) to generate comprehensive symptom vocabularies and identify symptom information in EHR notes. We piloted this method with five diverse symptom concepts – *constipation*, *depressed mood*, *disturbed sleep*, *fatigue*, and *palpitations*.

Methods: First, we obtained synonym lists for each pilot symptom concept from the Unified Medical Language System. Then, we used two large bodies of text ($n=5,483,777$ clinical notes from Columbia University Irving Medical Center and $n=94,017$ PubMed abstracts containing Medical Subject Headings or key words related to the pilot symptoms) to further expand our initial vocabulary of synonyms for each pilot symptom concept. We used *NimbleMiner*, an open-source NLP tool, to accomplish these tasks. We evaluated *NimbleMiner* symptom identification performance by comparison to a manually annotated set of $n=449$ nurse- and physician-authored common EHR note types.

Results: Compared to the baseline Unified Medical Language System synonym lists, we identified up to 11 times more additional synonym words or expressions, including abbreviations, misspellings, and unique multi-word combinations, for each symptom concept. NLP system symptom identification performance was excellent (F-measure ranged from 0.80 to 0.96).

Discussion: Using our comprehensive symptom vocabularies and *NimbleMiner* to label symptoms in clinical notes produced excellent performance metrics. The ability to extract symptom information from EHR notes in an accurate and scalable manner has the potential to greatly facilitate symptom science research.

Keywords

signs and symptoms; natural language processing; electronic health records

Assessing, monitoring, interpreting, treating, and managing symptoms are central aspects of nursing care. Symptoms are subjective indications of disease and include concepts such as *pain*, *fatigue*, *disturbed sleep*, *depressed mood*, *anxiety*, *nausea*, *dry mouth*, *shortness of breath*, and *pruritus*. Many patients experience one or more symptoms related to a health condition and/or its treatment. Both individual symptoms and symptom clusters, defined as two or more co-occurring, related symptoms (Kim et al., 2005; Miaskowski et al., 2017), can be challenging to manage and influence patient's mood, psychological status, functional status, quality of life, disease progression, and survival (Armstrong, 2003; Kwekkeboom, 2016).

Consequently, *symptom science* is a preeminent focus of nursing research (Cashion et al., 2016). Symptom science centers on the patient symptom experience (National Institute of Nursing Research, n.d.). The patient's symptom experience encompasses multiple dimensions, including occurrence, severity, and distress or bother (Wong et al., 2017). The goal of symptom science is "to be able to precisely identify individuals at risk for symptoms and develop targeted strategies to prevent or mitigate the severity of symptoms" (Dorsey et al., 2019, p. 88). Symptom science considers a wide range of biological, social, societal, and environmental determinants of health (Dorsey et al., 2019).

Secondary data reuse from electronic health records (EHRs), that captures diverse patient symptoms, has the ability to increase the quantity and quality of symptom research. In particular, text-based clinical notes are a rich source of symptom information. Historically, patient symptom information has been manually extracted from notes by clinical experts. This process is labor intensive, time consuming, expensive, and most prominently, lacks the scalability necessary to extract symptom information from large quantities of notes for hundreds to thousands or even millions of patients from data stored in EHRs.

Novel data science approaches, including natural language processing (NLP), can help to overcome scalability challenges related to manual note review. NLP is "any computer-based algorithm that handles, augments, and transforms natural language so that it can be represented for computation" (Yim et al., 2016) and is used to extract information, capture meaning, and detect relationships from language free text through the use of defined language rules and relevant domain knowledge (Doan et al., 2014; Fleuren & Alkema, 2015; Wang, Wang, et al., 2018; Yim et al., 2016).

Members of our team recently synthesized the literature on the use of NLP to process or analyze symptom information from EHR notes (Koleck et al., 2019). This systematic review revealed that NLP systems, methods, and tools are currently being used to extract information from diverse EHR notes (e.g., admission documents, discharge summaries, progress notes, nursing narratives) written by a variety of clinicians (e.g., physicians, nurses) on a wide range of symptoms (e.g., *anxiety, chills, constipation, depressed mood, fatigue, nausea, pain, shortness of breath, weakness*) across clinical specialties (e.g., cardiology, mental health, oncology). However, the use of NLP to extract symptom information from notes captured in EHRs is still largely in the developmental phase. Moreover, the majority of previous work has focused on the use of symptom information for physician/medicine-focused tasks, predominantly disease prediction, rather than on the investigation of symptoms themselves. Because existing NLP systems, methods, and tools were developed for the purpose of disease prediction, they may be insufficient for symptom-focused tasks. As nurses, it is critical that we develop and use NLP approaches that are designed for the specific purpose of studying core nursing concepts of interest, including symptom documentation in EHR clinical notes.

However, the complexity of the symptom language used in clinical notes makes the application of NLP challenging. The presence of a single symptom concept (e.g., *fatigue*) can be indicated using many different synonym words and expressions (e.g., *feeling tired, drowsiness, energy loss, exhaustion, groggy, sleepy, sluggish, tires quickly, weary, etc.*)

within notes. The words and expressions used in real world symptom documentation typically go beyond those contained in standardized vocabularies (e.g., *wiped out*, *low energy*) and can include common misspellings (e.g., *fatugue*, *faituge*, *fatiuge*) and abbreviations (e.g., *tatt - tired all the time*). In addition, the presence of a symptom word or expression may not indicate that the patient is experiencing that symptom. For example, a symptom may be negated (e.g., *no fatigue*, *does not complain of fatigue*) or occurred in the past (e.g., *pmhx fatigue*, *not currently fatigued*).

Advances in NLP of clinical data can help resolve some of these major challenges. Specifically, a new generation of machine learning (ML) models, called language models (Mikolov et al., 2013), can help to discover synonym vocabularies from large bodies of text. For example, a recently developed open-source and free NLP software, *NimbleMiner*, enables users to mine clinical texts to rapidly discover large vocabularies of synonyms that include abbreviations and misspellings (Topaz, Murga, Bar-Bachar, McDonald, & Bowles, 2019). *NimbleMiner* was successfully applied to identify a diverse range of clinical concepts in clinical notes, including drug and alcohol abuse (Topaz, Murga, Bar-Bachar, Cato, & Collins, 2019) and patient fall history (Topaz, Murga, Gaddis, et al., 2019), among others. However, new NLP methods (like the one applied by *NimbleMiner*) have not been used to identify symptom information in clinical notes.

In this paper, we describe a method that utilizes standardized vocabularies, clinical expertise, and NLP tools (i.e., *NimbleMiner*) to generate comprehensive symptom vocabularies to identify symptom information in EHR clinical notes. We piloted this method using five diverse symptom concepts – *constipation*, *depressed mood*, *disturbed sleep*, *fatigue*, and *palpitations* – and report our evaluation of *NimbleMiner* symptom identification performance using the generated comprehensive symptom vocabularies compared to a manually annotated gold standard note set.

MATERIALS & METHODS

We completed two overarching research activities as part of this study: (1) vocabulary development and (2) evaluation of *NimbleMiner* symptom identification performance. We outline the steps used to generate the comprehensive symptom vocabularies to identify symptom information in EHR notes and our evaluation of the vocabularies and *NimbleMiner* symptom identification performance in Figure 1, with additional details in the text. This study was approved by the Columbia University Irving Medical Center Institutional Review Board.

NimbleMiner Natural Language Processing System

NimbleMiner (<https://github.com/mtopaz/NimbleMiner>) is an open-source and free NLP RStudio Shiny application (<https://shiny.rstudio.com/>) that enables users to mine clinical texts to rapidly discover large vocabularies of synonyms (Topaz, Murga, Bar-Bachar, McDonald, & Bowles, 2019). Briefly, to build vocabularies within *NimbleMiner*, the user imports a large body of relevant text and a preliminary list of words and expressions for a concept of interest. The software performs text preprocessing (e.g., removal of punctuation, modification of letter case) and converts frequently co-occurring words to 4-gram (i.e.,

up to four word) expressions using a phrase2vec algorithm (Topaz, Murga, Bar-Bachar, McDonald, & Bowles, 2019).

Then, *NimbleMiner* builds language models (i.e., statistical representations of a body of text) using a word embedding skip-gram implementation in an R statistical package called word2vec (Mikolov et al., 2013). The word embedding models use neighboring words to identify other potential synonyms (i.e., words or expressions that appear in the same context) for each imported word or expression. The user can iteratively accept (i.e., designate as a synonym) or reject (i.e., designate as an irrelevant term) words or expressions suggested by the system until no new synonyms are identified. Following discovery of synonyms, *NimbleMiner* is used to identify positive instances of a concept in text using regular expressions (i.e., specially encoded strings of text). *NimbleMiner* accounts for negated terms as well. For example, the software is able to identify expressions like *no palpitations* or *denies fatigue* as negated synonyms. While not a feature employed in this study, *NimbleMiner* can also use ML algorithms to create predictive models of whether text contains a concept of interest.

Vocabulary Development

Step 1. Identifying symptom concepts and developing preliminary lists of

synonyms: First, we reviewed a widely used medical terminology, Systematized Nomenclature of Medicine (SNOMED-CT, clinical findings category), to create a catalog of candidate symptom concepts. Candidate symptom concepts were reviewed by nurse clinician scientists. The nurse clinician scientists who participated in this study have extensive clinical and research expertise in symptoms and chronic conditions that rank among the leading causes of death and disability in the United States, specifically heart disease (SB), cancer (CM), diabetes (AS), and chronic lung disease (MG) (National Center for Chronic Disease Prevention and Health Promotion, n.d.). We identified a list of 57 unique candidate symptom concepts (see Supplemental Table 1 for a full list).

For the purposes of this study, we selected five diverse symptom concepts – *constipation*, *depressed mood*, *disturbed sleep*, *fatigue*, and *palpitations* – to pilot-test methods and evaluate *NimbleMiner* symptom identification performance. These five symptoms were chosen due to their varying degrees of conceptual complexity (i.e., how difficult a symptom concept is to clearly define and distinguish from other symptom concepts) and potential diversity of language used by clinicians to describe these symptoms. Next, we created a preliminary list of words and expressions (further called synonyms) for each of the symptom concepts using the Unified Medical Language System (UMLS). UMLS is a compendium of many health terminologies, including SNOMED, International Classification for Nursing Practice (ICNP), North American Nursing Diagnosis Association (NANDA International), and others (Bodenreider, 2004). Using the UMLS “synonyms” category that includes words and expressions used by different terminologies to describe a concept of interest, we extracted a list of synonyms for each of the five symptom concepts. The nurse clinician scientists had the opportunity to review these lists and make recommendations for changes (e.g., addition of synonyms, removal of synonyms). UMLS/expert-informed synonym lists for the five symptom concepts are displayed in Table 1.

Step 2. Building language models for synonym discovery: We used two large bodies of text to generate two corresponding language models in *NimbleMiner*: (1) EHR clinical notes and (2) PubMed abstracts. These two bodies of text, or corpora, were selected because they would allow us to extract a complementary and diverse range of synonyms. EHR clinical notes include clinical jargon terms while PubMed abstracts have more standardized synonyms used in the scientific literature (Topaz, Murga, Bar-Bachar, McDonald, & Bowles, 2019). For the EHR source, we obtained all available patient clinical notes ($n=5,483,777$) from the Columbia University Irving Medical Center Clinical Data Warehouse (CDW) authored between January 1, 2016 and December 31, 2016. These notes represent 1,449 unique note types from an array of specialties (e.g., internal medicine, psychiatry, cardiology, nephrology, neurology, surgery, obstetrics), settings (e.g., inpatient, emergency department, ambulatory), and members of the healthcare team, including nurses, physicians, physical therapists, occupational therapists, nutritionists, respiratory therapists, and social workers. Notes were from $n=238,026$ distinct patient medical record numbers. The number of notes per medical record number ranged from 1 to 2,372 ($M=23.04$, $SD=56.9$; median=9). Notes were authored by $n=9,863$ individuals. The number of notes written by a single clinician ranged from 1 to 9,900 ($M=538.1$, $SD=720.6$; median=282).

For the PubMed source, we extracted all available PubMed abstracts ($n=94,017$) containing Medical Subject Headings (MeSH) or key words related to the pilot symptoms of interest. We used the following query on May 24, 2019, to identify PubMed abstracts:

("constipation"[MeSH Terms] OR "constipation"[All Fields]) OR (disturbed[All Fields] AND ("sleep"[MeSH Terms] OR "sleep"[All Fields])) OR (("consciousness disorders"[MeSH Terms] OR ("consciousness"[All Fields] AND "disorders"[All Fields]) OR "consciousness disorders"[All Fields] OR ("depressed"[All Fields] AND ("affect"[MeSH Terms] OR "affect"[All Fields] OR "mood"[All Fields])) OR ("fatigue"[MeSH Terms] OR "fatigue"[All Fields]) OR palpitations[All Fields] AND (hasabstract[text] AND "humans"[MeSH Terms] AND English[lang]).

We converted text from each source into a single text (.txt) file and uploaded to *NimbleMiner*. We used *NimbleMiner* to perform preprocessing, convert frequently co-occurring words to 4-gram expressions, and build language models.

Step 3. Generating comprehensive vocabularies for each symptom concept: We imported the UMLS/expert-informed preliminary synonyms for each pilot symptom (Table 1) into *NimbleMiner*. Based on the language models built in Step 2, *NimbleMiner* suggested 50 similar terms for each imported synonym. Two individuals with expertise in symptoms (TK & MH) independently reviewed and accepted or rejected suggested synonym words or expressions for each symptom concept of interest. This process of *NimbleMiner* suggesting similar words/expressions and the reviewer accepting/rejecting words/expressions was iteratively repeated for chosen words/expressions until no new relevant synonyms were identified by the reviewers. The two reviewers compared lists of words/expressions and discussed discrepancies. When the two reviewers could not come to an agreement on whether or not a word/expression should be included as a symptom concept synonym, an

adjudicator (MT) made the final decision. The output of this step was a comprehensive vocabulary for each symptom concept.

Evaluation of *NimbleMiner* symptom identification performance—Finally, we evaluated *NimbleMiner* symptom identification performance for the five pilot symptoms. To perform this evaluation, we created a gold standard set of manually annotated clinical notes. In order to increase the probability of positive occurrences of the pilot symptoms in the notes, we first queried the Columbia University Irving Medical Center CDW for patients ($n=133$) with International Classification of Diseases 10th Revision (ICD10) diagnosis billing codes in 2016 for 4 of the pilot symptoms or conditions closely related to a pilot symptom. Included ICD10 codes for each symptom are displayed in Supplemental Table 2. There were $n=119$ patients with one or more notes ($n=27,300$). For these patients, we extracted the ten most frequent nurse- and physician-authored note types ($n=4,827$), including: miscellaneous nursing, medicine follow-up free text, hematology/oncology attending follow-up, ambulatory hematology/oncology nursing assessment, emergency department nursing assessment, medicine resident progress, emergency department disposition, discharge summary, nursing adult admission history, and emergency department adult pre-assessment notes.

Then, we randomly selected $n=349$ notes, with the counts for each of the ten note types in proportion to their frequency in the overall set of notes. Specific counts for each of the common note types were as follows: miscellaneous nursing – $n=87$, medicine follow-up free text – $n=45$, hematology/oncology attending follow-up – $n=38$, ambulatory hematology/oncology nursing assessment – $n=35$, emergency department nursing assessment – $n=30$, medicine resident progress – $n=27$, emergency department disposition – $n=26$, discharge summary – $n=21$, nursing adult admission history – $n=20$, and emergency department adult pre-assessment notes – $n=20$. Because documentation of *depressed mood* and *palpitations* was limited in these notes, we decided to review and manually label an additional randomly selected $n=50$ psychiatric consult notes and $n=50$ cardiology free text notes. Thus, our gold standard note set contained a total of 449 clinical notes. The number of notes per unique patient ($n=93$) in the gold standard note set ranged from 1 to 30 ($M=4.8$, $SD=5.7$; median=3). The number of notes authored by an individual clinician ($n=299$) ranged from 1 to 10 ($M=1.5$, $SD=1.3$; median=1).

Two nurses (TK & SM) manually reviewed each note and annotated the note for the presence or absence of each of the five pilot symptoms. Relative observed agreement (i.e., percent agreement between raters) and inter-rater reliability (i.e., Cohen's kappa statistic) were calculated for each symptom. Level of agreement for Cohen's kappa is interpreted as: 0–0.20 – *none*, 0.21–0.39 – *minimal*, 0.40–0.59 – *weak*, 0.60–0.79 – *moderate*, 0.80–0.90 – *strong*, and >0.90 – *almost perfect* (McHugh, 2012). The two nurses plus a third nurse adjudicator (MT) discussed non-agreement to achieve consensus. Overall, the number of notes with positive occurrence of each symptom by manual review was as follows: *constipation* – $n=49$, *depressed mood* – $n=62$, *disturbed sleep* – $n=77$, *fatigue* – $n=84$, and *palpitations* – $n=11$.

Then, we used *NimbleMiner* to identify symptoms in the $n=449$ gold standard note set. We compared the *NimbleMiner* identification labels to the manual annotation and calculated recall (i.e., *NimbleMiner*'s ability to identify all notes with positive occurrence of a particular symptom; $\frac{\text{true positives}}{\text{true positives} + \text{false negatives}}$), precision (i.e., proportion of notes with a particular symptom endorsed by *NimbleMiner* that are actually positive occurrences; $\frac{\text{true positives}}{\text{true positives} + \text{false positives}}$) and F-measure (i.e., a measure of test accuracy that considers both precision and recall; $F_1 = 2 * \frac{\text{precision} * \text{recall}}{\text{precision} + \text{recall}}$) for each symptom. F measures range from 0 (poor precision and recall) to 1 (perfect precision and recall). We further reviewed all instances of disagreement between *NimbleMiner* identification labels and gold standard annotations.

RESULTS

Vocabulary Development

We identified additional synonym words and expressions for each symptom concept beyond the inputted UMLS/expert-informed synonym list (Table 2). The increase in synonym vocabulary size ranged from double for *disturbed sleep* to almost an 11 times increase for *constipation*. The synonym words and expressions represented abbreviations (e.g., *palps*), misspellings (e.g., *palpations*, *palipations*), and unique multi-word combinations (e.g., *feels heart racing*, *dyspnea palpitations*, *dizziness palpitations*, *palpitations holter monitor*). For all symptom concepts, a number of synonyms were identified by both users as well as additional unique synonym words or expressions identified by one of the two users. The comprehensive vocabularies for *constipation*, *depressed mood*, *disturbed sleep*, *fatigue*, and *palpitations* are available in Supplemental Table 3.

Evaluation of *NimbleMiner* Symptom Identification Performance

Manual annotation of the gold standard clinical note set—Relative observed agreement and inter-rater reliability for manual annotation of the $n=449$ gold standard note set were as follows for each symptom: *constipation* – 92.4%, $k=0.604$; *depressed mood* – 89.3%, $k=0.557$; *disturbed sleep* – 90.0%, $k=0.630$; *fatigue* – 92.9%, $k=0.734$; and *palpitations* – 94.0%, $k=0.377$. Instances of disagreement were related to extrapolation of medication (e.g., senna or docusate for *constipation*) or procedure (e.g., cardioversion for *palpitations*) documentation to the active presence of a symptom. Our team ultimately decided that the symptom itself needed to be documented in the clinical notes to be considered a positive occurrence.

Automated identification of symptoms with *NimbleMiner*—*NimbleMiner* symptom identification performance metrics for each pilot symptom are reported in Table 3. Recall ranged from 0.81 to 0.99; precision ranged from 0.75 to 0.96; and F_1 ranged from 0.80 to 0.96, all indicating good or excellent system performance.

The most common reason for false positive symptom identification was due to a symptom term being relatively far from a negation term (e.g., *no complaint of pain*, *diarrhea*, *constipation*). Other common causes of false positives included the negation term not being

included in the software vocabulary (e.g., *pmhx, never exhibited, prior history of, ho, no recent, not a current problem*); non-relevant usage of a symptom term (e.g., *sluggish referring to pupil response not fatigue, depression referring to a diagnosis and not current mood state*); and reference to a potential medication side effect rather than an active problem (e.g., *may cause drowsiness*). On the other hand, lacking synonym words and expressions for *disturbed sleep* (e.g., *did not sleep well last night, unable to sleep, patient reports change in sleep*) and *constipation* (e.g., *no BM, has not had a bm in several days, no significant BM, patient without BM, indication constipation*) resulted in the vast majority of false negatives.

DISCUSSION

In this paper, we describe a method that leverages standardized vocabularies, clinical expertise, and NLP tools to create comprehensive vocabularies to identify symptom information documented within EHR notes. The general steps for comprehensive symptom vocabulary development included: 1) identifying symptom concepts and developing preliminary lists of synonyms, 2) building language models for synonym discovery, and 3) generating comprehensive vocabularies for each symptom concept. We piloted this method using five symptom concepts with varying degrees of conceptual complexity and symptom term diversity – *constipation, depressed mood, disturbed sleep, fatigue, and palpitations* – and evaluated *NimbleMiner* symptom identification performance for the pilot symptoms against a manually annotated gold standard note set.

Considering that an F-measure reaches its best value at 1 (i.e., perfect precision and recall) and worst at 0, we observed excellent symptom identification performance with the pilot comprehensive symptom vocabularies via the *NimbleMiner* system. F-measures ranged from 0.80 for *constipation* to 0.96 for *fatigue*. It is difficult to compare these results to the literature as extraction/symptom identification performance for individual symptoms are limited and context specific. The systematic review that Koleck et al. (2019) conducted on the use of NLP to process or analyze symptom information from EHR notes identified studies that featured the pilot symptom concepts of *constipation* (Chase et al., 2017; Hyun et al., 2009; Iqbal et al., 2017; Ling et al., 2015; Nunes et al., 2017; Tang et al., 2017; Wang, Hripcsak, et al., 2009), *depressed mood* (Chase et al., 2017; Divita et al., 2017; Jackson et al., 2017; Ling et al., 2015; Tang et al., 2017; Wang, Chused, et al., 2008; Weissman et al., 2016; Zhou et al., 2015), *fatigue* (Chase et al., 2017; Friedman et al., 1999; Hyun et al., 2009; Iqbal et al., 2017; Matheny et al., 2012; Tang et al., 2017; Wang, Hripcsak, et al., 2009), and *disturbed sleep* (Chase et al., 2017; Divita et al., 2017; Iqbal et al., 2017; Jackson et al., 2017; Tang et al., 2017; Wang, Chused, et al., 2008; Wang, Hripcsak, et al., 2009; Zhou et al., 2015). No NLP investigations specifically named *palpitations*. Out of these studies, three reported NLP system performance metrics for individual symptoms. Iqbal et al. (2017) created a tool, the Adverse Drug Event annotation Pipeline (ADEPt), to identify adverse drug events from notes; *constipation* (precision=0.91, recall=0.91, $F_1=0.91$) and *insomnia* (precision=0.84, recall=0.93, $F_1=0.88$) were included as adverse events. Matheny and colleagues (2012) developed a rule-based NLP algorithm for infectious symptom detection and reported metrics for *fatigue* (precision=1.00, recall=0.79, $F_1=0.89$). In addition, Jackson et al. (2017) developed a suite of models, comparing a ConText algorithm with or without ML, to identify symptoms of severe mental illness from routine

mental health encounters. Symptom model performance against gold standards was reported for the *depressed mood* synonyms of *anhedonia*, *apathy*, and *low mood* (precision=0–0.96, recall=0–1.00, F_1 =0–0.96) and the *disturbed sleep* synonyms of *disturbed sleep* and *insomnia* (precision=0.70–0.90, recall=0.84–0.99, F_1 =0.80–0.94).

While performance for individual symptom concepts was not reported, a study by Divita et al. (2017) had the closest goal to our own – to develop an NLP algorithm that reliably identified mentions of positively asserted symptoms from the free text of clinical notes. Their scalable pipeline features the V3NLP framework, rule-based symptom annotators, and automated ML in Weka and was designed using notes from the Veterans Affairs' Corporate Data Warehouse. Model performance on a test set of notes was precision=0.80, recall=0.74, and F-measure=0.80. Overall, our method achieved comparable performance to these studies.

While we observed excellent performance, we manually reviewed all discrepancies between our annotated gold standard and *NimbleMiner* symptom identification. This in-depth exercise revealed additional modifications that could be made to improve performance, including increasing the negation distance, incorporating additional negation terms (e.g., *past medical history*, *no recent*), defining irrelevant terms (e.g., *sluggish pupil response*) and expanding vocabulary terms (e.g., *change in sleep*, *unable to sleep*). The irrelevant terms and additional ML features of *NimbleMiner* may assist with the latter two modifications. Incorporation of irrelevant terms may improve symptom identification performance for symptom term instances of non-relevant usage. For example, we could include *sluggish pupil response* as an irrelevant expression to correct this instance of *sluggish* being identified as an occurrence of *fatigue*. Likewise, we could include *major depressive disorder* as an irrelevant expression to distinguish between a diagnosis of depression and current *depressed mood* state. Nevertheless, it may never be possible to create an exhaustive list of synonym or irrelevant words or expressions for a symptom concept. Strategies such as training ML models (e.g., random forest algorithms) that can be used to predict whether a note contains the symptom concept of interest based on characteristics of a note, rather than matching a specific word or expression, may further improve performance (Topaz, Murga, Gaddis, et al., 2019). ML may also help to capture aspects of the symptom experience beyond presence or absence, including frequency, intensity, distress, and meaning (Armstrong, 2003).

This study had a number of strengths, including a text corpus comprising approximately 5.5 million notes from a variety of specialties, settings, and clinicians and over 90,000 relevant PubMed abstracts. Yet, all clinical notes included in this study were obtained from a single medical center. The generalizability of the comprehensive symptom vocabularies will need to be tested, potentially refined, and validated using data from additional medical centers. Another significant strength of this study was the evaluation of *NimbleMiner* symptom identification performance against a manually annotated gold standard note set from patients with diagnosis billing codes for pilot symptoms or conditions closely related to a pilot symptom. This process helped to ensure that we could test *NimbleMiner* symptom identification performance on adequate numbers of positive occurrences of pilot symptoms. However, we did limit the gold standard note set and pilot symptom identification evaluation to the 10 most frequent nurse- and physician-authored note types. We do not have

strong reason to believe that performance would be drastically different with other note types, especially since all notes were used to generate words and expressions for the comprehensive symptom vocabularies, but this assumption was not evaluated formally. In addition, our evaluation of the *NimbleMiner* system was limited to five symptom concepts. Pilot symptom concepts were selected by clinical experts based on conceptual complexity and the diversity of language used by clinicians to describe the symptom concept. *NimbleMiner* symptom identification performance may be different for symptom concepts not included in this pilot study (e.g., *pain*, *anxiety*, *nausea*).

In conclusion, symptoms are a core concept of nursing interest. A great need exists for vocabularies and NLP tools developed specifically for nursing-focused tasks, including studying symptom information documented in the EHR. Therefore, we generated and piloted comprehensive vocabularies for symptoms that can be used to identify symptom information from notes in the EHR. The use of the NLP tool, *NimbleMiner*, allowed us to enhance standardized vocabularies and clinical expert curation and leverage millions of text documents to develop “real world” EHR vocabularies of relevant words and expressions specific to symptoms. While opportunities exist for refinement, we successfully pilot tested our method and achieved excellent symptom identification performance for five diverse symptoms – *constipation*, *depressed mood*, *disturbed sleep*, *fatigue*, and *palpitations*. It is our hope that nurse scientists will be able to take advantage of the comprehensive symptom vocabularies that we are developing, and will continue to refine, for their own work. The ability to extract symptom information from EHR notes in an accurate and scalable manner has the potential to greatly facilitate symptom science research.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgement:

Research reported in this publication was supported by the National Institute of Nursing Research of the National Institutes of Health under Award Numbers K99NR017651 and P30NR016587. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. The authors thank Kathleen T. Hickey, EdD, FNP, ANP, FAHA, FAAN for her contributions to this project.

REFERENCES

- Armstrong TS (2003). Symptoms experience: A concept analysis. *Oncology Nursing Forum*, 30(4), 601–606. 10.1188/03.ONF.601-606 [PubMed: 12861321]
- Bodenreider O (2004). The Unified Medical Language System (UMLS): Integrating biomedical terminology. *Nucleic Acids Research*, 32(Database issue), 267–270. 10.1093/nar/gkh061
- Cashion AK, Gill J, Hawes R, Henderson WA, & Saligan L (2016). NIH Symptom Science Model sheds light on patient symptoms. *Nursing Outlook*, 65(5), 499–506. 10.1016/j.outlook.2016.05.008
- Chase HS, Mitrani LR, Lu GG, & Fulgieri DJ (2017). Early recognition of multiple sclerosis using natural language processing of the electronic health record. *BMC Medical Informatics and Decision Making*, 17(1), Article 24. 10.1186/s12911-017-0418-4 [PubMed: 28241760]
- Divita G, Luo G, Tran L-TT, Workman TE, Gundlapalli AV, & Samore MH (2017). General symptom extraction from VA electronic medical notes. *Studies in Health Technology and Informatics*, 245, 356–360. [PubMed: 29295115]

- Doan S, Conway M, Phuong TM, & Ohno-Machado L (2014). Natural language processing in biomedicine: A unified system architecture overview. *Methods in Molecular Biology* (Clifton, N.J.), 1168(Chapter 16), 275–294. 10.1007/978-1-4939-0847-9_16
- Dorsey SG, Griffioen MA, Renn CL, Cashion AK, Colloca L, Jackson-Cook CK, Gill J, Henderson W, Kim H, Joseph PV, Saligan L, Starkweather AR, & Lyon D (2019). Working together to advance symptom science in the precision era. *Nursing Research*, 68(2), 86–90. 10.1097/NNR.0000000000000339 [PubMed: 30640195]
- Fleuren WWM, & Alkema W (2015). Application of text mining in the biomedical domain. *Methods* (San Diego, Calif.), 74, 97–106. 10.1016/j.ymeth.2015.01.015
- Friedman C, Knirsch C, Shagina L, & Hripcsak G (1999). Automating a severity score guideline for community-acquired pneumonia employing medical language processing of discharge summaries. *Proceedings. AMIA Symposium*, 256–260.
- Hyun S, Johnson SB, & Bakken S (2009). Exploring the ability of natural language processing to extract data from nursing narratives. *Computers, Informatics, Nursing*, 27(4), 215–223. 10.1097/NCN.0b013e3181a91b58
- Iqbal E, Mallah R, Rhodes D, Wu H, Romero A, Chang N, Dzahini O, Pandey C, Broadbent M, Stewart R, Dobson RJB, & Ibrahim ZM (2017). ADEPT, a semantically-enriched pipeline for extracting adverse drug events from free-text electronic health records. *PloS One*, 12(11), Article e0187121. 10.1371/journal.pone.0187121 [PubMed: 29121053]
- Jackson RG, Patel R, Jayatilleke N, Kolliakou A, Ball M, Gorrell G, Roberts A, Dobson RJ, & Stewart R (2017). Natural language processing to extract symptoms of severe mental illness from clinical text: The Clinical Record Interactive Search Comprehensive Data Extraction (CRIS-CODE) project. *BMJ Open*, 7(1), Article e012012. 10.1136/bmjopen-2016-012012
- Kim H-J, McGuire DB, Tulman L, & Barsevick AM (2005). Symptom clusters: Concept analysis and clinical implications for cancer nursing. *Cancer Nursing*, 28(4), 270–282. [PubMed: 16046888]
- Koleck TA, Dreisbach C, Bourne PE, & Bakken S (2019). Natural language processing of symptoms documented in free-text narratives of electronic health records: A systematic review. *Journal of the American Medical Informatics Association*, 26(4), 364–379. 10.1093/jamia/ocy173 [PubMed: 30726935]
- Kwekkeboom KL (2016). Cancer symptom cluster management. *Seminars in Oncology Nursing*, 32(4), 373–382. 10.1016/j.soncn.2016.08.004 [PubMed: 27789073]
- Ling Y, Pan X, Li G, & Hu X (2015). Clinical documents clustering based on medication/symptom names using multi-view nonnegative matrix factorization. *IEEE Transactions on Nanobioscience*, 14(5), 500–504. 10.1109/TNB.2015.2422612 [PubMed: 26011887]
- Matheny ME, Fitzhenry F, Speroff T, Green JK, Griffith ML, Vasilevskis EE, Fielstein EM, Elkin PL, & Brown SH (2012). Detection of infectious symptoms from VA emergency department and primary care clinical documentation. *International Journal of Medical Informatics*, 81(3), 143–156. 10.1016/j.ijmedinf.2011.11.005 [PubMed: 22244191]
- McHugh ML Interrater reliability: The kappa statistic. (2012). *Biochemia Medica*, 22(3), 276–282. 10.11613/BM.2012.031 [PubMed: 23092060]
- Miaskowski C, Barsevick A, Berger A, Casagrande R, Grady PA, Jacobsen P, Kutner J, Patrick D, Zimmerman L, Xiao C, Matocha M, & Marden S (2017). Advancing symptom science through symptom cluster research: Expert panel proceedings and recommendations. *Journal of the National Cancer Institute*, 109(4), Article djw253. 10.1093/jnci/djw253
- Mikolov T, Corrado G, Chen K, & Dean J (2013). Efficient estimation of word representations in vector space (pp. 1–12). Presented at the International Conference on Learning Representations. National Center for Chronic Disease Prevention and Health Promotion. (n.d.). About chronic diseases. <https://www.cdc.gov/chronicdisease/about/index.htm>
- National Institute of Nursing Research. (n.d.). Spotlight on symptom science and nursing research. <https://www.ninr.nih.gov/researchandfunding/spotlights-on-nursing-research/symptomscience>
- Nunes AP, Loughlin AM, Qiao Q, Ezzy SM, Yochum L, Clifford CR, Gately RV, Dore DD, & Seeger JD (2017). Tolerability and effectiveness of exenatide once weekly relative to basal insulin among type 2 diabetes patients of different races in routine care. *Diabetes Therapy: Research, Treatment*

- and Education of Diabetes and Related Disorders, 8(6), 1349–1364. 10.1007/s13300-017-0314-z [PubMed: 28983857]
- Tang H, Solti I, Kirkendall E, Zhai H, Lingren T, Meller J, & Ni Y (2017). Leveraging Food and Drug Administration Adverse Event Reports for the automated monitoring of electronic health records in a pediatric hospital. *Biomedical Informatics Insights*, 9, Article 1178222617713018. 10.1177/1178222617713018 [PubMed: 28634427]
- Topaz M, Murga L, Bar-Bachar O, Cato K, & Collins S (2019). Extracting alcohol and substance abuse status from clinical notes: The added value of nursing data. *Studies in Health Technology and Informatics*, 264, 1056–1060. 10.3233/SHTI190386 [PubMed: 31438086]
- Topaz M, Murga L, Bar-Bachar O, McDonald M, & Bowles K (2019). NimbleMiner: An open-source nursing-sensitive natural language processing system based on word embedding. *Computers, Informatics, Nursing*, 37(11), 583–590. 10.1097/CIN.0000000000000557
- Topaz M, Murga L, Gaddis KM, McDonald MV, Bar-Bachar O, Goldberg Y, & Bowles KH (2019). Mining fall-related information in clinical notes: comparison of rule-based and novel word embedding-based machine learning approaches. *Journal of Biomedical Informatics*, 90, Article 103103. 10.1016/j.jbi.2019.103103 [PubMed: 30639392]
- Wang X, Chused A, Elhadad N, Friedman C, & Markatou M (2008). Automated knowledge acquisition from clinical narrative reports. *AMIA Annual Symposium Proceedings. AMIA Symposium*, 2008, 783–787.
- Wang X, Hripcsak G, Markatou M, & Friedman C (2009). Active computerized pharmacovigilance using natural language processing, statistics, and electronic health records: A feasibility study. *Journal of the American Medical Informatics Association*, 16(3), 328–337. 10.1197/jamia.M3028 [PubMed: 19261932]
- Wang Y, Wang L, Rastegar-Mojarad M, Moon S, Shen F, Afzal N, Liu S, Zeng Y, Mehrabi S, Sohn S, & Liu H (2018). Clinical information extraction applications: A literature review. *Journal of Biomedical Informatics*, 77, 34–49. 10.1016/j.jbi.2017.11.011 [PubMed: 29162496]
- Weissman GE, Harhay MO, Lugo RM, Fuchs BD, Halpern SD, & Mikkelsen ME (2016). Natural language processing to assess documentation of features of critical illness in discharge documents of acute respiratory distress syndrome survivors. *Annals of the American Thoracic Society*, 13(9), 1538–1545. 10.1513/AnnalsATS.201602-131OC [PubMed: 27333269]
- Wong ML, Paul SM, Cooper BA, Dunn LB, Hammer MJ, Conley YP, Wright F, Levine JD, Walter LC, Cartwright F, & Miaskowski C (2017). Predictors of the multidimensional symptom experience of lung cancer patients receiving chemotherapy. *Supportive Care in Cancer*, 25(6), 1931–1939. 10.1007/s00520-017-3593-z [PubMed: 28160076]
- Yim W-W, Yetisgen M, Harris WP, & Kwan SW (2016). Natural language processing in oncology: A review. *JAMA Oncology*, 2(6), 797–804. 10.1001/jamaoncol.2016.0213 [PubMed: 27124593]
- Zhou L, Baughman AW, Lei VJ, Lai KH, Navathe AS, Chang F, Sordo M, Topaz M, Zhong F, Murrall M, Navathe S, & Rocha RA (2015). Identifying patients with depression using free-text clinical documents. *Studies in Health Technology and Informatics*, 216, 629–633. [PubMed: 26262127]

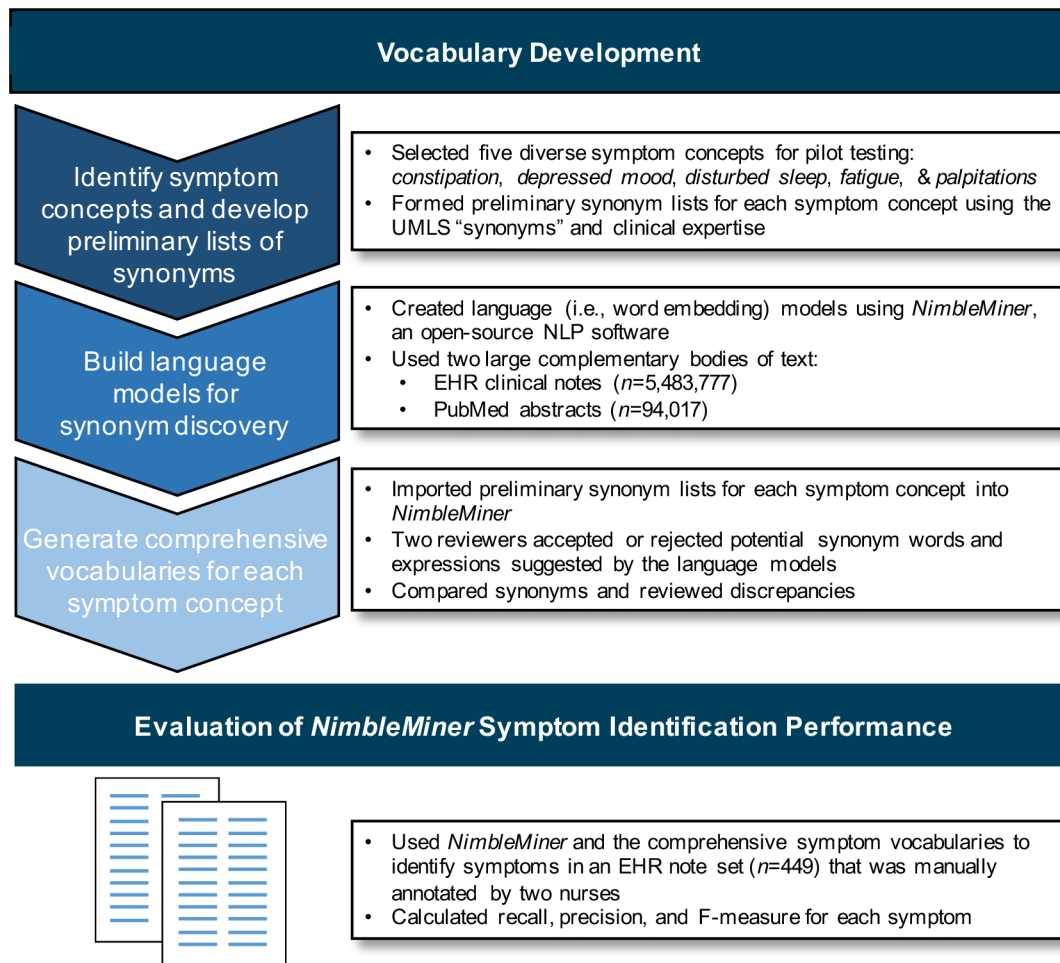


Figure 1.

Steps used to generate the comprehensive symptom vocabularies for identifying symptom information in EHR notes and to evaluate the vocabularies and *NimbleMiner* symptom identification performance

Table 1

UMLS/expert-informed synonym lists for the five pilot symptom concepts

Constipation	Depressed Mood	Disturbed Sleep	Fatigue	Palpitations
constipate	affect lack	awakening early	daytime somnolence	chest symptom palpitation
constipated	affect unhappy	awakening early morning	decrease in energy	heart irregularities
constipating	affects lack	bad dream	decreased energy	heart palpitations
constipation	anhedonia	bad dreams	drowsiness	heart pounds
costiveness	anhedonias	bizarre dreams	drowsy	heart racing
defecation difficult	apathetic	bothered by difficulty sleeping	easy fatigability	heart races
defaecation difficult	apathetic behavior	broken sleep	energy decreased	heart throb
difficult defaecation	apathetic behaviour	cannot get off to sleep	energy loss	heart throbbing
difficult defecation	apathy	chronic insomnia	excessive daytime sleepiness	palpitation
difficultly defecating	cannot see a future	complaining of insomnia	excessive daytime somnolence	palpitations
difficulty defaecating	decreased interest	complaining of nightmares	excessive sleep	racing heart
difficulty in defecating	decreased mood	complaining of vivid dreams	excessive sleepiness	rapid heart beat
difficulty in defaecating	demoralisation	delayed onset of sleep	excessive sleepiness during day	
difficulty in ability to defaecate	demoralization	difficult sleeping	excessive sleepiness during the day	
difficulty in ability to defecate	depressed	difficulty sleeping through the night	excessive sleeping	
difficulty to defaecate	depressed mood	difficulties sleeping	exhaustion	
difficulty to defecate	depressed state	difficulty falling asleep	exhausted	
difficulty opening bowels	depressing	difficulty getting to sleep	extreme exhaustion	
difficult passing motion	depression	difficulty in sleep initiation	extreme fatigue	
difficulty passing stool	depressions	difficulty in sleep maintenance	fatigability	
fecal retention	depression emotional	difficulty sleep	fatigue	
have been constipated	depression mental	difficulty sleeping	fatigued	
have constipation	depression mental function	difficulty staying asleep	fatigues	
	depression moods	disturbance in sleep behavior	fatiguing	
	depression psychic	disturbance in sleep behaviour	feel drowsy	
	depression symptom	disturbed sleep	feel fatigue	
	depressive state	disturbances sleep	feel fatigued	

Constipation	Depressed Mood	Disturbed Sleep	Fatigue	Palpitations
	depressive symptom	disturbances of sleep/insomnia	feel tired	
	depressive symptoms	dysnystaxis	feeling drowsy	
	despair	early awakening	feeling exhausted	
	diminished pleasure	early morning awakening	feeling of total lack of energy	
	emotional depression	early morning waking	fatigue extreme	
	emotional indifference	early waking	feeling tired	
	emotionally apathetic	fitful sleep	get tired easily	
	emotionally cold	frequent night waking	groggy	
	emotionally detached	frightening dreams	had a lack of energy	
	emotionally distant	have nightmares	hypersomnia	
	emotionally subdued	hyposomnia	I feel fatigued	
	feeling blue	initial insomnia	I have a lack of energy	
	feeling despair	insomnia	increased fatigue	
	feeling depressed	insomnia matutinal	increased need for rest	
	feeling down	insomnia chronic	increased sleep	
	feeling empty	insomnia late	increased sleeping	
	feeling helpless	insomnia vesperal	lack of energy	
	feeling hopeless	interrupted sleep	lacking energy	
	feeling isolated	interrupting sleep	lacking in energy	
	feeling lonely	keeps waking up	lacks energy	
	feeling of loss of feeling	late insomnia	lethargic	
	feeling lost	light sleep	lethargy	
	feeling low	light sleeping	loss of energy	
	feeling of despair	lights sleeping	quickly exhausted	
	feeling of hopelessness	hard to sleep through night	sleep excessive	
	feeling of sadness	hard to sleep through the night	sleep too much	
	feeling powerless	matutinal insomnia	sleepiness	
	feeling sad	middle insomnia	sleeping too much	
	feeling sad or blue	my sleep was restless	sleepy	

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Constipation	Depressed Mood	Disturbed Sleep	Fatigue	Palpitations
	feeling trapped	nightmares	sluggish	
	feeling unhappy	nightmares	sluggishness	
	feeling unloved	night wake	somnolence	
	feeling unwanted	night wakes	somnolent	
	feelings of hopelessness	night waking	time tired	
	feelings of worthlessness	not getting enough sleep	tired	
	feels there is no future	other insomnia	tired all the time	
	helplessness	poor quality sleep	tatt	
	hopeless	poor sleep	tired feeling	
	hopelessness	poor sleep pattern	tired out	
	I feel sad or blue	primary insomnia	tired time	
	indifference	problems with sleeping	tiredness	
	indifferent mood	prolonged sleep	tires quickly	
	lack of interest	restless sleep	tire easily	
	lethargic	restless sleeping	too much sleep	
	lethargy	short of sleep	weariness	
	listless	short sleeping	weary	
	listless behavior	sleep difficult	washed out	
	listless behaviour	sleep difficulties	worn out	
	listless mood	sleep disorder insomnia		
	listlessness	sleep disorder insomnia chronic		
	loss of capacity for enjoyment	sleep disorders		
	loss of hope for the future	sleep disturbance		
	loss of interest	sleep disturbances		
	loss of pleasure	sleep disturbed		
	loss of pleasure from usual activities	sleep dysfunction		
	lost feeling	sleep maintenance insomnia		
	low mood	sleep is restless		
	melancholia	sleep was restless		

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

Constipation	Depressed Mood	Disturbed Sleep	Fatigue	Palpitations
	melancholic	sleeping difficulty		
	melancholy	sleeping difficulties		
	mental depression	sleeping disturbances		
	miserable	sleep restless		
	mood depressed	sleeplessness		
	mood depression	terrifying dreams		
	mood depressions	terminal insomnia		
	morose mood	tosses and turns in sleep		
	morosity	tossing and turning during sleep		
	negative about the future	trouble falling asleep		
	no hope for the future	trouble sleeping		
	nothing matters	unpleasant dreams		
	powerlessness	vesperal insomnia		
	sad	vivid dreams		
	sad mood	wakes and cannot sleep again		
	sadness	wakes early		
	stuporous	waking during night		
	symptoms of depression	waking too early		
	torpid	waking night		
	unhappiness	wakes up at night		
	unhappy	wakes up during night		
	worthless			
	worthlessness			

Table 2

Counts of symptom concept synonym words or expressions

Symptom concept	Preliminary UMLS/ expert-informed synonyms	Additional synonyms identified by both reviewers	Additional unique synonyms identified by Reviewer 1	Additional unique synonyms identified by Reviewer 2	Total additional synonyms	Percent increase in synonyms
<i>Constipation</i>	23	22	19	15	56	243%
<i>Depressed mood</i>	108	494	61	55	610	565%
<i>Disturbed sleep</i>	106	92	35	0	127	120%
<i>Fatigue</i>	75	278	52	35	365	487%
<i>Palpitations</i>	12	111	21	11	143	1192%

Table 3

NimbleMiner symptom identification performance metrics

Symptom concept	Recall	Precision	F-measure
<i>Constipation</i>	0.83	0.78	0.80
<i>Depressed mood</i>	0.96	0.91	0.93
<i>Disturbed sleep</i>	0.81	0.96	0.87
<i>Fatigue</i>	0.97	0.95	0.96
<i>Palpitations</i>	0.99	0.75	0.83

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript