Comprehensive identification of Long Covid articles with human-in-the-loop machine learning

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Highlights
• We propose a semi-automated classification framework for creating scientific literature collections with reduced need for human labels.
• Our framework integrates automated classifiers of varying accuracy to provide a reliable classification for each article and flags articles where human effort is needed.
• We use our framework to identify PubMed articles on Long Covid, also known as post-acute sequelae of SARS-CoV-2.
• As of November 2021, we identify 5,645 articles relevant to Long Covid – 75.8% of which do not mention Long Covid by name – and have collected 496 synonymous terms for Long Covid.

The bigger picture
Locating articles that refer to novel entities is generally challenging since keyword searches suffer from limited results and low accuracy without broadly supported terminology. However, comprehensively identifying articles on emerging diseases such as Long Covid is critical due to their importance for public health. While Long Covid causes ongoing multisystemic symptoms in a substantial percentage of COVID-19 survivors, it is still incompletely understood and lacks effective treatments. We developed an iterative human-in-the-loop framework to comprehensively identify articles relevant to Long Covid. Our framework integrates multiple classifiers with complementary views and varying accuracy into a single model that reliably predicts the relevance of each article to Long Covid and its priority for manual annotation.

Summary
A significant percentage of COVID-19 survivors experience ongoing multisystemic symptoms that often affect daily living, a condition known as Long Covid or post-acute-sequelae of SARS-CoV-2 infection. However, identifying Long Covid articles is challenging since articles refer to the condition using a variety of less common terms or refrain from naming it at all. We developed an iterative human-in-the-loop machine learning framework designed to effectively leverage the data available and make the most efficient use of human labels. Specifically, our approach combines data programming with active learning into a robust ensemble model. Evaluating our model on a holdout set demonstrates over three times the sensitivity of other methods. We apply our model to PubMed to create the Long Covid collection, and demonstrate that (1) most Long Covid articles do not refer to Long Covid by any name (2) when the condition is named, the name used most frequently in the biomedical literature is Long Covid, and (3) Long Covid is associated with disorders in a wide variety of body systems. The Long Covid
collection is updated weekly and is searchable online at the LitCovid portal: https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=e_condition.LongCovid

Graphical Abstract

Keywords
Long Covid · post-acute sequelae of SARS-CoV-2 infection · COVID-19 · text classification · machine learning · weak supervision · data programming · active learning · natural language processing

Data Science Maturity
DSML 2: Proof of concept: Data science output has been formulated, implemented, and tested for one domain/problem.

Introduction
Literature collections such as LitCovid provide a critical resource as scientific understanding expands (Chen et al., 2021), serving as a centralized access point for reliable and comprehensive information on COVID-19. Early in the pandemic, however, some survivors of acute COVID-19 began reporting symptoms lasting much longer than the amount of time then reported for clinical recovery. These patients – many of whom were themselves healthcare professionals or researchers – turned online for support, naming the condition Long Covid, as a contraction of long-term COVID illness (Callard and Perego, 2021).

In May 2020, a patient-led group published the first survey of long-term symptoms of COVID-19 (Patient Led Research Collaborative, 2020). The incidence rates reported for Long Covid vary widely; from 9% to
81% according to one meta-analysis (Chen et al., 2022), though this is partially due to differing definitions of Long Covid (Deer et al., 2021). Nevertheless, there is now substantial evidence that a significant percentage of COVID-19 survivors experience ongoing multisystemic symptoms (Davis et al., 2021; Nalbandian et al., 2021a; Nalbandian et al., 2021b; Taquet et al., 2021), including respiratory issues (Hayes et al., 2021), cardiovascular disease (Xie et al., 2022), cognitive impairment (Douaud et al., 2022), and profound fatigue (Carfì et al., 2020). For many patients, these symptoms affect daily living or returning to work (Havervall et al., 2021; Sivan et al., 2021). Moreover, subsequent research has confirmed patient reports that Long Covid occurs even in patients with low risk of death (Blomberg et al., 2021; Havervall et al., 2021) and in younger patients, including children (McFarland et al., 2022). However most of the morbidity burden of COVID-19 (i.e., healthy years of life lost) is in COVID-19 survivors, not fatalities (Smith, 2021).

Sequelae of viral infections have been widely discussed in the literature: Poliovirus (Aston, 1992), Varicella-zoster virus (Freer and Pistello, 2018), Epstein-Barr virus (Bjornevik et al., 2022), Zika virus (Brasil et al., 2016), West Nile virus (Patel et al., 2015) and SARS-CoV (Moldofsky and Patcai, 2011; Ngai et al., 2010) have all been implicated in long-term sequelae, sometimes many years after the initial infection. However, Long Covid remains incompletely understood, despite evidence for several theories (Proal and VanElzakker, 2021), and effective treatments are lacking. Definitions of Long Covid used in the literature vary substantially (Deer et al., 2021), impairing the ability of research to build on previous work (Akbarialiabad et al., 2021), though consensus-based case definitions are emerging (Soriano et al., 2021). The published literature uses a wide variety of terms to refer to Long Covid, but more commonly refers to the condition with a description rather than a name. Querying for articles relevant to Long Covid is therefore challenging: narrow, precise queries such as “post-acute sequelae of SARS-CoV-2 infection” return limited results while broad queries such as “post COVID symptoms” return many false positives.

In this work, our goal is to identify biomedical research articles useful for researchers, clinicians, and patients/advocates interested in Long Covid. We created our Long Covid collection using human-in-the-loop machine learning (Monarch, 2021), an approach that applies active learning to iteratively identify relevant instances within a collection while requiring only a small fraction of the articles to be annotated manually. We combine this human-in-the-loop approach with the weakly supervised method data programming to integrate a set of task-specific noisy signals, called labeling functions (Ratner et al., 2016). We further developed three novel extensions to data programming.

Of the 5,645 articles we identify as relevant to Long Covid in the LitCovid collection through November 15, 2021, 75.8% do not mention Long Covid directly, making identification via query difficult. We evaluated our automated prediction model on a held-out set of manually annotated articles, demonstrating an ROC AUC of 0.8530. We further compared our approach to several other approaches to identifying Long Covid articles, demonstrating an over 3-fold improvement in sensitivity. The Long Covid Collection is available within the LitCovid portal, a widely used literature hub with over 200,000 articles specific to COVID-19.
Results
We describe our results in two parts. First, we describe the validation of our framework with an inter-annotator agreement study and measure the accuracy of our results against several comparison approaches. Second, we describe the Long Covid Collection created using our framework.

Validation: Inter-Annnotation Agreement
We performed a small manual inter-annotator agreement study to verify the repeatability of the annotator guidelines, provided in the Supplementary Materials. We randomly selected 100 of the articles previously annotated by the primary annotator (RL, a bioinformatician with previous annotation experience). These were labeled by the senior annotator (JW, an M.D./Ph.D.). Each article was labeled as relevant or not relevant, using the full text of the article as needed. The annotators agreed on 87 articles (61 Relevant, 26 Irrelevant) for an inter-annotator agreement of 87.0%.

Validation: Comparison Methods
We compared our results to several other collections on Long Covid. The CoronaCentral resource contains articles related to several coronaviruses, including SARS-CoV-2, with automated predictions for both topics and various entities (Lever and Altman, 2021). We consider articles annotated with both SARS-CoV-2 and the Long Haul topic as Long Covid articles according to CoronaCentral. PubMed Clinical Queries uses predefined filters to help users perform and refine specialized searches. The queries for COVID-19 are intended to limit results to articles on SARS-CoV-2 with a particular topic; we use the Long COVID query, which is listed in full in the Supplementary Materials. We created a query using MeSH terms by combining COVID-19 or SARS-CoV-2 and terms reflecting the post-acute phase, also listed in full in the Supplementary Materials. We also created several textual queries based on the most common Long Covid terms, as shown in Figure 1.

Validation: Evaluation
The evaluation set contains 1,119 positive articles and 773 negative articles. We evaluate the results using sensitivity and specificity, which can be visualized using the Receiver Operating Characteristic (ROC) curve, and can be summarized as the area under the ROC curve (AUC) (Fawcett, 2006). Since the comparison approaches provide only binary predictions, we binarize our results for comparison by thresholding at a prediction of 0.7. The ROC curve for our results and the sensitivity/specificity points for all comparison approaches can be seen in Figure 1. The area under the curve (AUC) is 0.8530.
Figure 1. Receiver Operating Characteristic (ROC) curve of our results. Shown with the sensitivity/specificity points for our results thresholded at prediction ≥ 0.7 and several alternative collections of articles relevant to Long Covid. The area under the curve (AUC) is 0.8530.

While the comparison methods provide high specificity, the highest sensitivities are for the post-covid symptoms query (0.2073) and CoronaCentral (0.1868), while the sensitivity of our thresholded results is 0.7096.

Resource Description
As of mid-November 2021, the Long Covid Collection contained 5,645 articles. The Long Covid grammar-based named entity recognizer identified 3,166 mentions of Long Covid, representing 496 unique phrases (after normalizing case and punctuation); these are summarized in Figure 2. Despite the flexibility of the grammar, 75.8% of the articles in the Long Covid Collection do not contain an identifiable term for Long Covid. This is commonly caused by the article referring to Long Covid using a description rather than by name; we discuss this further in the Discussion section.
Figure 2. Terms for Long Covid found most frequently by the Long Covid grammar. The grammar found a total of 3,166 mentions of Long Covid, representing 496 unique phrases, ignoring capitalization and punctuation.

Naming Trend for Long Covid over Time

Figure 3 shows the naming trend over time, with all articles relevant to Long Covid listed as either mentioning Long Covid directly (i.e., using the term Long Covid), mentioning Long Covid but using a different term, or not mentioning Long Covid by name.

Figure 3. Trend over time of terms used to refer to Long Covid in articles relevant to Long Covid. Articles that mention Long Covid use the name Long Covid at least once. Articles that use an alternative term
mention Long Covid at least once via identifiable synonym. Articles that do not mention Long Covid do not contain an identifiable term for Long Covid. All articles listed are relevant to Long Covid.

Analysis of Entities Mentioned
PubTator is a web-based system providing annotations for six entity types: genes/proteins, genetic variants, diseases, chemicals, species, and cell lines (Wei et al., 2019). We compared the annotation rate for entities annotated by PubTator in the Long Covid Collection and LitCovid. We found that the entities that showed a statistically significant difference (p < 0.01, Fisher’s exact test) were primarily disorders that appear more frequently in the Long Covid Collection than in the general COVID-19 literature. We further removed disorders specific to COVID-19. Figure 4A visualizes the 25 disorders that appear most frequently in the Long Covid collection in a dendrogram, clustered according to the number of ancestors in common in the MeSH hierarchy. The great variety of body systems affected demonstrates that Long Covid is a multisystemic condition; we discuss this further in the Discussion section.

Analysis of Topic Clusters
We use the probabilistic distributional clustering (PDC) algorithm to identify topics within the Long Covid Collection (Islamaj et al., 2020). PDC uses terms, phrases, and MeSH terms occurring within a collection as input and utilizes their probability of co-occurrence to partition the set of input features into disjoint groups. Documents can then be scored with respect to each topic identified and may receive a high score for more than one topic. Figure 4B shows the 13 most frequent topics identified by the PDC clustering algorithm, with pairwise associations scaled according to the number of articles in common. The names for each topic cluster are manually generated but represent the most common phrases in the cluster.

Figure 4. (A) Dendrogram of the disorders that appear most frequently in the Long Covid collection and whose annotation rate is greater than in the general COVID-19 literature (p < 0.01, Fisher’s exact test). Disorders are clustered according to the number of ancestors in common in the Medical Subject
Headings (MeSH) hierarchy. (B) Chord diagram of the most frequent topics in the Long Covid collection, identified with the PDC algorithm, and their pairwise associations. Cluster names are manually generated but reflect the most common phrases in the cluster. Long Covid is a complex, multisystemic, condition that causes a wide variety of potentially serious complications.

Discussion

COVID-19 has caused widespread mortality and strained healthcare systems worldwide (Chan et al., 2021). Estimates of the overall morbidity burden show, however, that most of the burden lies in COVID-19 survivors (Smith, 2021). While estimates of the prevalence of Long Covid vary, a recent meta-analysis shows that the prevalence of symptoms beyond four weeks is quite high: 43% (Chen et al., 2022). Moreover, the effects experienced many years or decades later are yet unknown. Continuing research into Long Covid is critical and the Long Covid Collection allows these articles to be identified comprehensively and analyzed as a set.

We note that while Long Covid is the most common term used in the literature to refer to Long Covid (see Figure 2), its use does not appear to be accelerating (see Figure 3). Moreover, the percentage of articles which are relevant to Long Covid but do not refer to it using an identifiable term also appears to be stable. This suggests that a lack of terminological consensus will remain for some time. Unfortunately, this reluctance to name the condition likely makes it more difficult for consensus to build: articles that rely on descriptions will be more difficult to locate since automated recognition of descriptions is known to be much more difficult than names (Leaman et al., 2020). Given the critical need to build on existing research, we recommend authors refer to Long Covid by name, using one of the most common terms.

Our methods are automated and do not produce perfect accuracy. However, this is partially due to inherent ambiguities. For example, it is sometimes difficult to label articles based on the title and abstract, such as determining whether a reference to COVID-19 patients refers to patients who had COVID-19 previously or patients who currently have acute COVID-19 [e.g. PMID 35043098]. Unfortunately, the full text is often not available. However, the descriptions authors use to refer to Long Covid are sometimes beyond the ability of the grammar to recognize. This is often due to some specific qualification, such as an anatomical system. For example, the phrase “residual respiratory impairment after COVID-19 pneumonia” [PMID 34273962] strongly suggests a respiratory form of Long Covid but could not be recognized by the grammar. A more advanced recognition technique may be able to recover some additional mentions, though identifying these articles comprehensively with keyword queries will remain difficult. A more advanced technique may also help reduce false positives in the grammar, though these are quite rare. For example, “... how long COVID-19 (SARS-CoV-2) survives ...” [PMID 32967479] includes the phrase “long COVID” but does not refer to Long Covid.

While it is difficult to provide a definitive discussion of how many articles must be annotated to provide high coverage, we note that our framework already provides an AUC of 0.7069 using only the labeling functions that do not require training. We performed a series of experiments iteratively rerunning article selection and found that 1,000 manually annotated articles reliably produces a model with an AUC of over 0.80 (data not shown). In this work we also intended to provide a reliable, comprehensive collection of articles on Long Covid; we therefore proceeded to manually annotate most of the relevant articles and a nearly equal number of irrelevant articles. Note, however, that this still results in a significant annotation savings compared with manual annotation: we annotated approximately 3.9% of
the articles in LitCovid, representing an annotations savings of 96.1%. We therefore believe that our framework reduces the need for manual annotations when identifying high-variation terminology.

The analysis of entities mentioned demonstrate clearly that Long Covid is a multisystemic condition: the disorders mentioned more frequently in the Long Covid collection than in LitCovid affect most major organ systems. Fatigue is listed, as would be expected given that it is a primary symptom, as well as several neurological conditions and cognitive dysfunctions. Interestingly, several symptoms closely associated with COVID-19 are seen to appear more frequently in connection with Long Covid than COVID-19, such as dyspnea and olfaction disorders. Finally, the topic clustering offers a slightly different perspective, but again strongly underscores that Long Covid is multisystemic. We see two large clusters on the lung, lung function, and pulmonary fibrosis, but the next largest cluster is on cardiovascular effects. We next see substantial clusters on olfactory & gustatory dysfunction, multisystem inflammatory syndrome, and, perhaps surprisingly, thyroid function. Only the cluster on prolonged viral shedding appears to be related to mechanism rather than symptoms.

Limitations & Future Work
Long Covid is a complex, multisystemic condition that is currently not completely understood, and research progress is likely to motivate some new terminology. Should this occur, we anticipate that our framework will continue to identify new terms. Moreover, we anticipate that the Long Covid collection itself will remain relevant for some time even if a strong consensus builds and the level of terminological variation drops significantly. Nevertheless, Long Covid remains an area of active research, and new developments are expected.

Our definition of Long Covid is primarily time-based, while many of the studies in the literature that discuss sequelae of COVID-19 are primarily concerned with a body system. This is particularly the case with neurological effects, which are prevalent in Long Covid but may also appear much earlier, even as the initial manifestation of infection. Our annotators noted that many articles could not be labeled from just the title and abstract; this is primarily because of the condition that symptoms must be present at least a month after initial infection. Moreover, our combination of a broad definition and short timeframe (one-month post-infection) implies the inclusion of some post-COVID conditions with an acute presentation, notably multisystem inflammatory syndrome in children (MIS-C) and mucormycosis. However, these conditions do share some elements, such as immune system dysregulation. Again, Long Covid remains an area of active research and updates are expected.

Experimental Procedures
Lead contact
Further information and requests for resources should be directed to the lead contact, Zhiyong Lu (zhiyong.lu@nih.gov).

Materials availability
This study did not generate any new unique materials.

Methods
We created the Long Covid Collection using a human-in-the-loop machine learning process with the goal of minimizing human effort while creating an accurate and well-calibrated classifier. In our usage, an
active learning process iteratively chooses articles for the human annotators to judge for relevance, which are then used to improve an automated system. The updated system is then used to select a new set of articles for annotation, focusing on articles where the automated system is uncertain, and the process repeats. This iterative process produces a high probability of identifying all articles relevant to Long Covid without the need to manually review every article.

We provide an overview of our framework in Error! Reference source not found., which illustrates the data flow for the three high level processes used by our system. The first process, model creation, prepares the labeling functions (some of which require training data), retrieves a label for each article from each labeling function, and creates the ensemble model using data programming. The second process, article prediction, uses the model to predict the relevance of every article. The third process, article annotation, uses the model to identify uncertain predictions; articles with high uncertainty are then prioritized for manual annotation. One quarter of annotated articles are reserved for evaluation and the remainder are added to the training data.

**Figure 5.** System overview, illustrating the flow of data for the three primary system processes: model creation, article prediction and article annotation.

**Annotation Guidelines**

Following the broadest early definition with substantial support (Centers for Disease Control and Prevention, 2020), we defined Long Covid to be ongoing symptoms at least four weeks after initial symptoms. We therefore considered an article to be relevant to Long Covid if it meets the following two criteria: First, the article must consider adverse effects resulting from COVID-19, i.e., SARS-CoV-2 infection. Second, the article must report outcomes or symptoms over a timeframe that includes at least four weeks post-infection. Note that articles do not need to mention Long Covid by name to be relevant, and that relevant articles may discuss persistent symptoms in the full text rather than the abstract. We provide the full annotation guidelines in the Supplementary Materials.

**Human-in-the-Loop Process Overview**

Our goal is to identify all PubMed articles relevant to Long Covid. Since LitCovid contains all published PubMed articles relevant to SARS-CoV-2 or COVID-19 (Chen et al., 2021), the task becomes classifying each article in LitCovid as relevant or irrelevant to Long Covid.
The automated system employs a semi-supervised approach, allowing predictions to be made even with very little labeled data. The system combines multiple relevance signals – some of which are created with supervised classification – using the weakly supervised framework data programming (Ratner et al., 2016). These relevance signals, called labeling functions, are derived from disparate data sources, producing multiple views of the data which are sometimes contradictory. While similar to stacking, data programming creates the ensemble model without training data, and triplet methods provide a closed form solution that does not require iterative training. We extend data programming to allow probabilistic labeling functions (rather than only binary), to improve reliability of the ensemble model, and to provide uncertainty scores.

In human-in-the-loop machine learning, data points can be selected for human annotation based on either diversity sampling or uncertainty sampling (Monarch, 2021). In diversity sampling, the data is clustered and instances are chosen to ensure that each cluster is represented. Uncertainty sampling, on the other hand, prioritizes instances closest to the decision boundary or instances with the largest variation in predictions. Our initial analysis showed fast improvements with uncertainty sampling, with no additional benefit with diversity sampling. Our framework therefore prioritizes articles for annotation when close to the decision boundary or when the automated predictions show high variation.

**Data Programming**

While supervised machine learning requires abundant training data, data programming creates a model by aggregating weaker forms of supervision (Ratner et al., 2016). This creates an ensemble model, similar to the machine learning method stacked generalization (Wolpert, 1992), also known as stacking, but without using additional training data. In the data programming paradigm, the practitioner creates labeling functions – task-specific functions that imperfectly label instances – instead of labeling instances. Labeling functions may take many forms, including rule-based patterns, dictionary lookups, and noisy supervised classifiers. The labeling functions are applied to a large amount of unlabeled data, and the agreement rates between the labeling functions are then used to infer the accuracy of each labeling function. The accuracies for each labeling function then form the parameters of a generative model that can be used to label new data points, applying a small amount of knowledge – in the form of labeling functions – to accurately label a large amount of data. Note that various forms of noise – including missing values and disagreements – are anticipated and handled by the framework.

Since human-in-the-loop methods begin with very little labeled data, applying data programming within a human-in-the-loop approach would seem to be ideal. However, the human-in-the-loop approach requires the automated system to be repeatedly retrained, which is inconvenient despite the simplicity of the generative model due to the large data sizes involved. Data programming with triplet methods makes repeated retraining unnecessary by directly estimating the accuracy of each labeling function using a closed form solution (Fu et al., 2020). This solution requires only calculating the pairwise agreement rates between a triplet of labeling functions; it can be extended to an arbitrary number of labeling functions by iterating through all possible triplets and averaging the results.

Specifically, given a triplet of binary labeling functions $\mathcal{L}_1, \mathcal{L}_2, \text{ and } \mathcal{L}_3$ of the form $\mathcal{L}(x) \in \{0, 1\}$:

$$\text{accuracy}(\mathcal{L}_1) = \frac{1}{2} \sqrt{\text{agree}(\mathcal{L}_1, \mathcal{L}_2) \cdot \text{agree}(\mathcal{L}_1, \mathcal{L}_3)} + \frac{1}{2} \frac{\text{agree}(\mathcal{L}_2, \mathcal{L}_3)}{\text{agree}(\mathcal{L}_1, \mathcal{L}_3)} + \frac{1}{2}$$
Where we define agree for a pair of labeling function as:

\[
agree(L_1, L_2) = \frac{1}{|X|} \sum_{x \in X} equal(L_1(x), L_2(x))
\]

And we define equal as:

\[
equal(L_1(x), L_2(x)) = \begin{cases} 
1, & \text{if } L_1(x) = L_2(x) \\
-1, & \text{if } L_1(x) \neq L_2(x)
\end{cases}
\]

Note that in the previous definition the labeling functions \(L(x)\) have binary values. We extend the accuracy calculation to handle probabilistic labeling functions \(\hat{L}(x) \in [0, 1]\). We first define sample \((x)\) to be a function that discretizes its input \(x \in [0, 1]\) by returning the value 1 with probability \(x\) and returning 0 with probability \(1 - x\). We can then define the equal function for probabilistic labeling functions by averaging over many samples, each of which has discrete binary values. We note that the result converges to a closed form solution as the number of samples approaches infinite, specifically:

\[
equal(\hat{L}_1(x), \hat{L}_2(x)) = \lim_{n \to \infty} \frac{1}{n} \sum_{i=1}^{n} equal(sample(\hat{L}_1(x)), sample(\hat{L}_2(x)))
\]

\[
= (2\hat{L}_1(x) - 1) \cdot (2\hat{L}_2(x) - 1)
\]

Also note that under this formulation, a labeling function that cannot provide a prediction for any given input may abstain by returning exactly 0.5.

The accuracy of each labeling function can be estimated by forming a triplet with any other two labeling functions. Since there is an abundance of labeling functions, we gather many estimates for each labeling function by using all available pairs and use their mean as the final accuracy estimate. However, we improve the reliability of the accuracy estimates by ignoring pairs of labeling functions whose agreement may be due to chance. We model the agreement between a pair of labeling functions as a binomial distribution, where the number of trials is the number of instances and the number of successes is the number of instances where the labeling functions agree. We calculate a confidence interval on the agreement rate between each pair of labeling functions and discard the pairs where the confidence interval includes 0.5. Our implementation uses the Wald method at the 95% confidence level.

Prediction and Uncertainty Sampling

Given the vector of accuracies for each labeling function, \(a\), and the vector of labeling function values \(l\) for a given article, the prediction \(p \in [0, 1]\) is:

\[
p = \frac{1}{1 + e^{-x}}, \text{where } x = \sum_i l_i \times \log \frac{a_i}{1 - a_i}
\]

We recalibrate the predictions of the generative model using the mean and standard deviations of the articles manually annotated positively and negatively.

In a human-in-the-loop approach, the automated model provides both predictions as well as prioritizing instances for manual annotation (Monarch, 2021). We prioritize articles for manual annotation by identifying articles whose predictions are uncertain. We use two approaches for uncertainty sampling, specifically distance to threshold and prediction variation. Under distance to threshold, instances with
predictions closer to the decision boundary have higher uncertainty; given a prediction \( p \) and a threshold \( t \), the distance to the threshold is \( \text{dist} = \text{abs}(p - t) \). We support uncertainty sampling via variation by running the data programming inference multiple times, masking 50% of the labeling functions during each run, then calculating the inter-quartile range of the predictions for each instance (\( iqr \)). Our final selection criterion combines the distance to the threshold and variation calculations, choosing the unlabeled instances that simultaneously minimize \( \text{dist} \) and maximize \( iqr \).

**Description of Labeling Functions**

Data programming with triplet methods requires the assumption that the labeling functions are conditionally independent given the class (Fu et al., 2020). We use eight types of labeling functions, chosen for providing complementary views. Error! Reference source not found. describes the labeling functions briefly; they are fully described in the Supplemental Materials. Several of the labeling function types (LitSuggest, MeSH headings, entity annotations) require training data. Manually annotated data is split into four parts: one part is reserved for evaluation. The remainder are used to train three independent labeling functions for each labeling function type.

*Table 1.* Labeling functions used to identify articles relevant to Long Covid. Complete descriptions of each labeling function are provided in the Supplemental materials.

| Name                        | Description                                                                 | Requires Training Data |
|-----------------------------|-----------------------------------------------------------------------------|------------------------|
| Long Covid grammar          | A purpose-built grammar-based named entity recognition system to identify mentions of Long Covid. Uses the full text, if available | No                     |
| LitSuggest, trained by query| Predictions from the LitSuggest web-based literature curation tool (Allot et al., 2021), trained using a query for positives and random articles for negatives | No                     |
| LitSuggest, trained on annotations | Predictions from the LitSuggest web-based literature curation tool (Allot et al., 2021), trained using the annotated training data | Yes                    |
| PubTator entity annotations | Entities from the PubTator annotation system (Wei et al., 2019), using the full text, if available | Yes                    |
| MeSH headings               | Medical Subject Headings indexed by the NLM indexing team, if available       | Yes                    |
| CoronaCentral Long-Haul Topic | Articles from the CoronaCentral portal (Lever and Altman, 2021), annotated with the Long Haul topic and one or more mentions of SARS-CoV-2 | No                     |
| CoronaCentral Entity Annotations | Entity annotations provided by the CoronaCentral portal                     | Yes                    |
| Bias                        | Labels all articles as probably not relevant                               | No                     |

**Data and Code Availability**

The Long Covid collection is publicly available at the LitCovid portal: https://www.ncbi.nlm.nih.gov/research/coronavirus/docsum?filters=e_condition.LongCovid. The classification and mentions for each article are also publicly available: https://ftp.ncbi.nlm.nih.gov/pub/lu/LongCovid/. The code used in this study is available for review at
https://ftp.ncbi.nlm.nih.gov/pub/lu/LongCovid/SourceCode. This will be shared publicly through GitHub upon acceptance.

Acknowledgements
This research was supported by the Intramural Research Program of the National Library of Medicine, National Institutes of Health.

Author contributions
Conceptualization: RL and ZL. Overall methodology, software, and analysis: RL. Supervision: ZL. Annotation guidelines: RL, RI, JW, AA, and QC. Data curation and validation: RL and JW. PDC analysis: RI. LitCovid resources and software: AA and QC. LitSuggest software: AA. Drafted initial manuscript: RL. All authors reviewed, edited, and approved of the final manuscript.

Declaration of interests
The authors declare no competing interests.

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