THE LANCET
Digital Health

Supplementary appendix

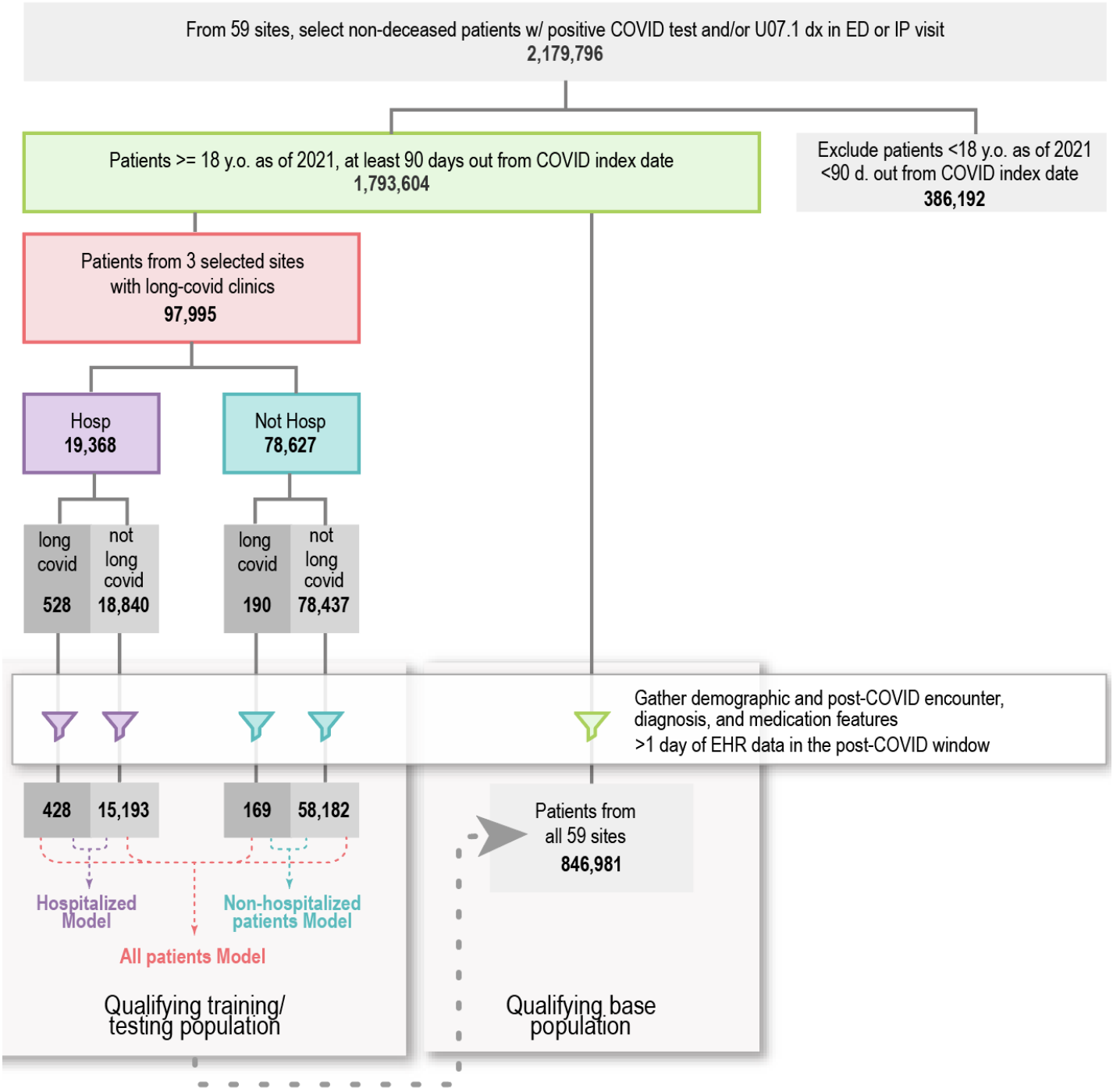
This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Pfaff ER, Girvin AT, Bennett TD, et al. Identifying who has long COVID in the USA: a machine learning approach using N3C data. *Lancet Digit Health* 2022; published online May 16. https://doi.org/10.1016/ S2589-7500(22)00048-6.

Supplemental Material

Contents

Supplemental Figure 1: Cohort Selection Flow Diagram



Supplemental Methods

Feature Engineering

The feature tables used as inputs for each model are made up of patient age, sex, healthcare utilization metrics, pre-COVID-19 comorbidities, post-COVID-19 diagnoses, and post-COVID-19 medications. Curation methods for each of these domains are described here. All OMOP concept sets and feature engineering code described here are available at https://github.com/NCTraCSIDSci/n3c-longcovid or by author request via the N3C Enclave, according to the N3C governance and regulatory policies.

Healthcare utilization metrics

In order to calculate a utilization metric for each patient, we first determine the number of days in each patient's post-COVID-19 "window." By our definition, this window begins 45 days after the patient's COVID-19 index date and ends 320 days later, for a total of 365 days after the COVID-19 index date. Thus, every patient has a window of 320 days (though the dates differ for each patient, based on their COVID-19 index dates). The exception to this is the long-COVID clinic patients used to train the model; their post-COVID-19 window ends on the day before their first long-COVID clinic visit date, as supplied by the three sites.

Outpatient utilization ratios for each patient are calculated as:

$$\frac{\text{(\# unique calendar days patient has an outpatient encounter in the post-COVID-19 window)}}{\text{(\# days in the patient's post-COVID-19 window)}}$$

Inpatient utilization ratios for each patient are calculated as:

$$\frac{\text{(sum of lengths of stay for all inpatient visits in the post-COVID-19 window)}}{\text{(\# days in the patient's post-COVID-19 window)}}$$

Pre-COVID-19 comorbidities

We added indicator variables to flag whether each patient had one or more of the following comorbidities *prior* to their COVID-19 index date: diabetes, chronic kidney disease, congestive heart failure, chronic pulmonary disease. A patient was flagged as having one of these comorbidities if they had a diagnosis code for that condition on two or more occasions (distinct calendar days) prior to their COVID-19 index date.

Post-COVID-19 diagnoses

The OMOP data model uses SNOMED CT as a standard vocabulary for diagnoses. SNOMED CT is multi-hierarchical, meaning that a single child concept can have many parent concepts. Here, we "rolled up" SNOMED-coded diagnoses to parent-level features for use in our ML models. Because the various levels of the SNOMED hierarchy are not consistent in granularity, automated roll up can lead to uninformative terms that are not useful model features (e.g. "disorder of body system"), and these uninformative concepts can appear as model features if enough of their child concepts have some importance in classification.

Informative terms that should be included based on clinical relevance are sometimes present at the same hierarchical level as these less informative terms. It is therefore not possible to roll up all SNOMED terms using a specific hierarchical level (i.e., roll up diagnoses to the fourth level down from the root). We therefore devised a computational approach to rolling up terms that lessens uninformative terms. A summary of the approach follows:

- Extract a dataset of all SNOMED CT child terms (i.e., the diagnosis terms used in the patient data) matched with two levels of parent terms (i.e., the child term's parent(s) and the parent(s)' parent(s)).
- Exclude the following parent concepts entirely, due to non-informativeness: "105721009 - General problem AND/OR complaint," '64572001 - Disease," "363296001 - Sequelae of disorders classified by disorder-system," "362977000 - Sequela," "58184002 - Recurrent disease," "55607006 - Problem,"

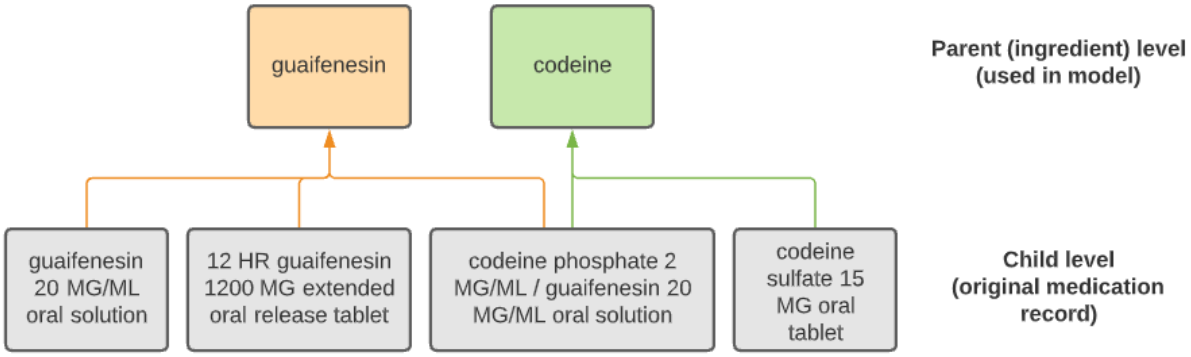
"2704003 - Acute disease," "27624003 - Chronic disease," "116223007 - Complication." Child conditions that roll up to these parent terms remain in the data, but will not roll up to one of these terms.
- Exclude parent terms that contain the words "right" or "left", which enables all child terms that specify laterality to be rolled up to a non-lateral parent.
- Exclude parent terms that contain the words "finding," "disorder of," or "by site" (which are generally generic, low-information terms), *unless* removal of the parent term would leave a child term without a viable parent term.
- Use the remaining set of parent terms in place of the child terms in the model.

Despite this computational pruning, there is still some concept duplication within our ML model because closely related concepts (which may be equivalent by some definitions) can exist in different branches of the hierarchy (e.g. "dyspnea" and "difficulty breathing"). These are inherent caveats of using ontologies and can be addressed through manual curation for future studies.

For each patient, we only counted conditions that newly occurred or occurred in greater frequency in the post-COVID-19 period compared to the pre-COVID-19 period. Finally, before running the model, we limited diagnosis features to those that were associated with at least 1% of the patients in our three-site subset. We first ran the model without this restriction to ensure this would not affect model performance, and noted our results were the same. We thus opted to add this restriction in order to render our models less computationally intensive.

Post-COVID-19 medications

As with diagnoses, we rolled up medication records to parent-level concepts in order to collapse related terms into single features. We used the OMOP vocabulary to roll up all medication records to the "ingredient" level. As shown in the example below, these roll-ups enable us to combine multiple forms of the same drug into a single term for modelling purposes. Combination drugs separately roll up to each of their ingredients, also shown below.



For each patient, we only counted medications that were newly prescribed in the post-COVID-19 period, with no records in the pre-COVID-19 period. Finally, before running the model, we limited medication features to those that were associated with at least 1% of the patients in our three-site subset. We first ran the model without this restriction to ensure this would not affect model performance, and noted our results were the same. We thus opted to add this restriction in order to render our models less computationally intensive.

Clinic Referral Practices

Though our IRB protocol does not enable us to identify the clinics that provided our long-COVID clinic patients, we can provide descriptions of each clinic's referral practices. We took this information into account when building our models, as practice differ among the three sites. However, the practices are similar enough to make them comparable.

Site	Referral Practice
1	Requires a physician referral. Accepts patients without a positive test, but asks the referring physician to explain why they suspect COVID-19 infection.
2	Requires a physician referral. Requests that patients have a positive test result on record.
3	Requires a physician referral. Testing requirements have changed over time. A record of a positive test was not required until approximately June 2021, at which point it became required.

Model Details

XGBClassifier models were trained using the python package XGBoost (https://xgboost.readthedocs.io/en/stable/python/python_api.html).

The following hyperparameters, selected with scikit-learn GridSearchCV, were used:

All Patients Model: colsample_bytree=0.1, gamma=0.4, learning_rate=0.09, max_depth=8, min_child_weight=0, n_estimators=400, subsample=0.9, random_state=42

Hospitalized Patients Model: colsample_bytree=0.2, gamma=0, learning_rate=0.1, max_depth=4, min_child_weight=0, n_estimators=100, subsample=0.6, random_state=42

Not Hospitalized Patients Model: colsample_bytree=0.4, gamma=0.5, learning_rate=0.01, random_state=42, subsample=1

All code used to define our cohort, build our models, and create the figures in this paper is open source and available at https://github.com/NCTraCSIDSci/n3c-longcovid.

Supplemental Table 1: Training and Test Set Patient Counts

		Training		Testing	
Model	**Patient subset**	**Long-COVID Clinic Patients**	**Not Long-COVID**	**Long-COVID Clinic Patients**	**Not Long-COVID**
All patients	Hospitalized	327	360	101	76
	Not hospitalized	125	134	44	45
Hospitalized	Hospitalized	327	360	101	76
Not-Hospitalized	Not hospitalized	125	134	44	45

Supplemental Table 2: Top 50 features in each model

The importance score for each feature is the sum of the importance of that feature for each patient. Mean values are the mean value of each feature across each group. All diagnosis and medication features are binary (1=yes, 0=no). For diagnoses, “yes” means that the patient had a greater number of occurrences of that diagnosis code in their post-COVID-19 window than their pre-COVID-19 window. For medications, “yes” means that the patient had one or more prescriptions for that medication in their post-COVID-19 window, and no record of that medication in their pre-COVID-19 window. Post-COVID-19 outpatient and inpatient utilization and age are continuous variables.

Table 2a. Top 50 all-patients model features, ranked by importance (SHAP value).

		Mean Values	
Feature	**Importance**	**Not Long-COVID**	**Predicted Long-COVID**
post-COVID-19 outpatient utilization	1,250.91	0.03	0.09
age	353.85	52.04	55.27
post-COVID-19 inpatient utilization	254.54	0.01	0.01
COVID-19 vaccine (med)	144.05	0.15	0.05
dyspnea (dx)	139.28	0.08	0.21
male sex	115.59	0.45	0.38
difficulty breathing (dx)	113.86	0.08	0.21
preexisting diabetes	89.02	0.12	0.17
albuterol (med)	79.19	0.07	0.12
dexamethasone (med)	75.89	0.11	0.04
metoprolol (med)	66.24	0.03	0.08
preexisting chronic kidney disease	62.61	0.08	0.12
melatonin (med)	53.18	0.06	0.10
hospitalized for COVID-19	50.27	0.73	0.72
hyperlipidemia (dx)	49.16	0.11	0.04
naloxone (med)	43.07	0.08	0.02
polyethylene glycol 3350 (med)	42.22	0.05	0.10
backache (dx)	42.01	0.06	0.02
preexisting chronic pulmonary disease	39.64	0.08	0.12
propofol (med)	38.14	0.09	0.04
increased lipids (dx)	34.36	0.10	0.04
triamcinolone (med)	34.15	0.04	0.02
heart failure (dx)	30.77	0.04	0.01
ibuprofen (med)	30.04	0.07	0.03
mixed hyperlipidemia (dx)	27.28	0.04	0.01
sennosides USP (med)	24.99	0.06	0.09
low back pain (dx)	24.87	0.05	0.01
nausea (dx)	24.17	0.04	0.02
cough (dx)	23.62	0.04	0.06
preexisting congestive heart failure	22.66	0.06	0.08
malaise (dx)	22.37	0.01	0.05
guaifenesin (med)	20.25	0.03	0.07
salmeterol (med)	19.52	0.01	0.03
aspirin (med)	18.99	0.05	0.04
soft tissue lesion (dx)	18.37	0.04	0.02
pain of truncal structure (dx)	18.32	0.12	0.08
pain (dx)	17.85	0.09	0.04
clinical finding (dx)	17.41	0.02	0.04
abdominal pain (dx)	16.80	0.05	0.01
acute respiratory disease (dx)	16.74	0.05	0.03
joint pain (dx)	15.65	0.04	0.01
renal failure syndrome (dx)	15.60	0.04	0.01
dyssomnia (dx)	15.07	0.02	0.03
amoxicillin (med)	14.72	0.04	0.02
hydralazine (med)	14.29	0.03	0.03
asthenia (dx)	14.03	0.04	0.03
diphenhydramine (med)	13.59	0.09	0.04
chest pain (dx)	13.41	0.05	0.07
tramadol (med)	13.15	0.06	0.02
hypertensive disorder (dx)	13.12	0.12	0.08

Table 2b. Top 50 non-hospitalized model features, ranked by importance (SHAP value)

		Mean Values	
Feature	**Importance**	**Not Long-COVID**	**Predicted Long-COVID**
post-COVID-19 outpatient utilization	77.58	0.02	0.07
difficulty breathing (dx)	25.95	0.04	0.29
age	18.26	41.94	48.46
dyspnea (dx)	14.01	0.04	0.29
male sex	11.26	0.37	0.24
COVID-19 vaccine (med)	9.72	0.22	0.08
post-COVID-19 inpatient utilization	2.27	0.00	0.00
oxycodone (med)	2.02	0.10	0.04
cough (dx)	1.72	0.01	0.10
prednisone (med)	1.41	0.04	0.04
arthralgia of the pelvic region and thigh (dx)	1.36	0.06	0.03
deficiency of micronutrients (dx)	1.18	0.01	0.03
polyethylene glycol 3350	1.18	0.04	0.02
albuterol (med)	1.12	0.02	0.13
dyssomnia (dx)	1.02	0.01	0.06
preexisting chronic pulmonary disease	1.02	0.05	0.16
ketorolac (med)	0.83	0.07	0.04
flumazenil (med)	0.76	0.06	0.01
vitamin D deficiency (dx)	0.67	0.01	0.03
metabolic disease (dx)	0.57	0.00	0.08
vitamin deficiency (dx)	0.50	0.01	0.03
hypoxemia (dx)	0.47	0.00	0.08
promethazine (med)	0.34	0.05	0.01
heart disease (dx)	0.31	0.01	0.03
vitamin disease (dx)	0.29	0.01	0.03
gabapentin (med)	0.29	0.03	0.05
clinical finding (dx)	0.28	0.00	0.06
diphenhydramine (med)	0.28	0.07	0.04
ibuprofen (med)	0.21	0.07	0.03
hydromorphone (med)	0.19	0.07	0.02
inflammation of specific body organs (dx)	0.17	0.07	0.06
benzocaine (med)	0.17	0.06	0.02
asthma (dx)	0.17	0.04	0.05
disorders of initiating and maintaining sleep (dx)	0.17	0.01	0.06
sleep disorder (dx)	0.15	0.04	0.10
hyperlipidemia (dx)	0.14	0.04	0.04
increased lipids (dx)	0.14	0.04	0.03
phenylephrine (med)	0.12	0.06	0.02
amoxicillin (med)	0.12	0.05	0.02
famotidine (med)	0.09	0.04	0.02
iohexol (med)	0.09	0.00	0.04
knee pain (dx)	0.08	0.04	0.00
chest pain (dx)	0.08	0.06	0.11
fentanyl (med)	0.07	0.07	0.06
pain of truncal structure (dx)	0.07	0.10	0.12
lactate (med)	0.07	0.09	0.05
muscle strain (dx)	0.00	0.01	0.01
musculoskeletal chest pain (dx)	0.00	0.02	0.00
muscle weakness (dx)	0.00	0.00	0.02
musculoskeletal finding (dx)	0.00	0.00	0.04

Table 2c. Top 50 hospitalized model features, ranked by importance (SHAP value)

		Mean Values	
Feature	Importance	Not Long-COVID	Predicted Long-COVID
post-COVID-19 outpatient utilization	744.99	0.03	0.10
post-COVID-19 inpatient utilization	161.05	0.01	0.01
age	159.54	55.80	57.87
COVID-19 vaccine (med)	54.84	0.12	0.04
dyspnea (dx)	51.04	0.09	0.18
dexamethasone (med)	48.34	0.12	0.03
hyperlipidemia (dx)	42.22	0.13	0.04
pain of truncal structure (dx)	41.66	0.12	0.06
difficulty breathing (dx)	41.49	0.09	0.18
preexisting diabetes	29.49	0.14	0.19
metoprolol (med)	28.42	0.04	0.09
preexisting chronic kidney disease	28.32	0.10	0.16
albuterol (med)	27.71	0.09	0.12
pain (dx)	24.53	0.10	0.03
polyethylene glycol 3350 (med)	24.06	0.05	0.12
naloxone (med)	21.45	0.08	0.01
backache (dx)	20.98	0.07	0.01
guaifenesin (med)	20.86	0.03	0.09
ondansetron (med)	19.62	0.15	0.09
male sex	18.78	0.48	0.44
heart failure (dx)	18.01	0.06	0.01
ibuprofen (med)	17.98	0.07	0.02
malaise (dx)	16.23	0.02	0.06
glucose (med)	15.82	0.08	0.09
insulin (med)	15.31	0.01	0.07
sennosides USP (med)	14.98	0.08	0.11
gastroesophageal reflux disease without esophagitis (dx)	14.93	0.08	0.03
breathing related sleep disorder (dx)	14.46	0.06	0.03
diabetes mellitus without complication (dx)	13.92	0.07	0.03
nausea (dx)	13.59	0.05	0.01
clinical history and observation findings (dx)	13.50	0.10	0.06
chlorhexidine (med)	12.92	0.01	0.04
iohexol (med)	12.61	0.05	0.08
sodium chloride (med)	12.24	0.14	0.12
Am. Soc of anesthesiologists physical status classification (dx)	11.97	0.08	0.04
phenylephrine (med)	11.71	0.06	0.03
increased lipids (dx)	11.54	0.12	0.04
bupivacaine (med)	10.77	0.05	0.00
quetiapine (med)	10.67	0.02	0.05
iopamidol (med)	10.46	0.07	0.02
melatonin (med)	10.46	0.08	0.13
renal failure syndrome (dx)	10.19	0.05	0.02
heart disease (dx)	10.04	0.07	0.04
fentanyl (med)	9.43	0.13	0.06
diphenhydramine (med)	9.32	0.10	0.04
hypoxemia (dx)	9.17	0.07	0.10
triamcinolone (med)	9.10	0.04	0.02
deficiency of micronutrients (dx)	8.74	0.04	0.03
ergocalciferol (med)	8.67	0.03	0.06
obstructive sleep apnea syndrome (dx)	8.57	0.06	0.02

N3C Data Partners

Data Partners with Released Data

Stony Brook University — U24TR002306 • University of Oklahoma Health Sciences Center — U54GM104938: Oklahoma Clinical and Translational Science Institute (OCTSI) • West Virginia University — U54GM104942: West Virginia Clinical and Translational Science Institute (WVCTSI) • University of Mississippi Medical Center — U54GM115428: Mississippi Center for Clinical and Translational Research (CCTR) • University of Nebraska Medical Center — U54GM115458: Great Plains IDeA-Clinical & Translational Research • Maine Medical Center — U54GM115516: Northern New England Clinical & Translational Research (NNE-CTR) Network • Wake Forest University Health Sciences — UL1TR001420: Wake Forest Clinical and Translational Science Institute • Northwestern University at Chicago — UL1TR001422: Northwestern University Clinical and Translational Science Institute (NUCATS) • University of Cincinnati — UL1TR001425: Center for Clinical and Translational Science and Training • The University of Texas Medical Branch at Galveston — UL1TR001439: The Institute for Translational Sciences • Medical University of South Carolina — UL1TR001450: South Carolina Clinical & Translational Research Institute (SCTR) • University of Massachusetts Medical School Worcester — UL1TR001453: The UMass Center for Clinical and Translational Science (UMCCTS) • University of Southern California — UL1TR001855: The Southern California Clinical and Translational Science Institute (SC CTSI) • Columbia University Irving Medical Center — UL1TR001873: Irving Institute for Clinical and Translational Research • George Washington Children's Research Institute — UL1TR001876: Clinical and Translational Science Institute at Children's National (CTSA-CN) • University of Kentucky — UL1TR001998: UK Center for Clinical and Translational Science • University of Rochester — UL1TR002001: UR Clinical & Translational Science Institute • University of Illinois at Chicago — UL1TR002003: UIC Center for Clinical and Translational Science • Penn State Health Milton S. 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Additional Data Partners Who Have Signed a DTA and Whose Data Release is Pending

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Ethics and Regulatory

The N3C data transfer to NCATS is performed under a Johns Hopkins University Reliance Protocol # IRB00249128 or individual site agreements with NIH.

Use of the N3C data for this study is authorised under the following IRB Protocols:

Site	IRB name	Exempted vs approved	Protocol number
University of Colorado	Colorado Multiple Institutional Review Board	approved	21–2759
Johns Hopkins University	Johns Hopkins Office of Human Subjects Research - Institutional Review Board	approved	IRB00249128
University of North Carolina	University of North Carolina Chapel Hill Institutional Review Board	exempt	21–0309
Stony Brook University	Office of Research Compliance, Division of Human Subject Protections, Stony Brook University	exempt	IRB2021–00098