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Assessment of the Performance of COVID-19 Diagnosis Code Using SARS-CoV-2 Test Results

Draft Protocol

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History of Modifications

Version	Date	Modification
1.0	1/15/2021	First Draft Protocol
2.0	1/29/2021	Second Draft Protocol
3.0	2/11/2021	Third Draft Protocol
4.0	2/28/2021	Fourth Draft Protocol
5.0	4/02/2021	Fifth Draft Protocol

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A Background

A new diagnosis code for coronavirus disease 2019 (COVID-19; International Classification of Diseases, Tenth Revision, Clinical Modification [ICD-10-CM] code U07.1) was introduced in the *ICD-10-CM Official Coding and Reporting Guidelines* on April 1, 2020.[1] Since its implementation, the U07.1 code has rapidly replaced the legacy ICD-10-CM code B97.29 (Other coronavirus as the cause of diseases classified elsewhere) in different care settings.[2] The accuracy of the U07.1 in identifying COVID-19 cases has been evaluated in the inpatient setting using billing codes in electronic health records (EHRs).[2] However, its performance has yet to be assessed in outpatient settings and in claims data.

Should performance of the diagnosis code be excellent, the presence and absence of COVID-19 diagnoses in claims data could be used to identify cases and noncases for the postauthorization evaluation of COVID-19 vaccine effectiveness. In such an evaluation, it is important to recognize that individuals who seek healthcare related to COVID-19 are likely different from those who do not, with respect to risk factors of contracting COVID-19, presence and severity of the symptoms, comorbidities, and healthcare consciousness. For example, infected individuals with mild or no symptoms may not seek healthcare or be tested; therefore, their claims data may not indicate that they had been infected.

This study aims to validate the U07.1 code in three study populations identified by healthcare encounters related to COVID-19. Within each study population, performance of the COVID-19 diagnosis code will be evaluated for the positive predictive value (PPV; the likelihood that a person with the diagnosis code recorded in administrative claims within a prespecified period actually has the disease) and the negative predictive value (NPV; the likelihood that a person without the diagnosis code recorded in administrative claims within a prespecified period does not have the disease). These performance metrics will inform internal validity (i.e., the extent of misclassification of COVID-19 cases) in future vaccine effectiveness studies in which COVID-19 disease status is based on the presence of a COVID-19 diagnosis among a defined care-seeking population.

This study will include several data sources with linked administrative claims and EHR data. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) reverse transcription polymerase chain reaction (RT-PCR) test results, also known as nucleic acid amplification tests (NAATs), on the linked EHR will serve as a reference method by which the claims-based diagnosis is evaluated.

B Study Aims

To estimate the PPV and NPV of the COVID-19 diagnosis code U07.1 in the three study populations identified in claims data using SARS-CoV-2 RT-PCR lab results as the gold standard in the linked EHRs.

The study populations include (1) individuals with at least one diagnosis code for COVID-19, related symptoms, or suspected exposures (study population 1 [SP1]); (2) individuals who received at least one SARS-CoV-2 RT-PCR test (SP2); and (3)

individuals who were hospitalized (SP3). Additional details on the study populations are provided in section C3.

C Methods

C1 Study Period and Observation Period

The study period will begin on April 1, 2020 and continue through the latest date for which claims data are at least 80% complete in the claims-EHR linked data sources. April 1, 2020 was selected because this is the date when the COVID-19 diagnosis code U07.1 was implemented in the United States, according to the Centers for Diseases Control and Prevention's (CDC's) recommended ICD-10-CM coding guidelines.[3] The observation period will start on October 1, 2019, to include a 6-month baseline period to capture underlying comorbidity information.

C2 Study Design

This study references several terms to specify three types of populations: *source population*, *study population*, and *validation sample*, which are defined as follows.

- ***Source population*:** Disease, test, and hospitalization episodes identified in the "parent" claims databases (e.g., IBM® MarketScan® Commercial Database, OneFlorida Data Trust Florida Medicaid, and Optum™ Clinformatics® Data Mart), from which a subset of patients was linked to their EHR records
- ***Study population*:** Disease, test, and hospitalization episodes identified in the claims portion of the claims-EHR linked databases (e.g., MarketScan commercial claims linked with Explorys® electronic medical records [EMRs] in the IBM MarketScan Explorys Claims-EMR Data Set [CED], OneFlorida Data Trust linked Medicaid claims-EHR, and OptumServe) that meet the continuous enrollment requirements specified in section C3
- ***Validation sample*:** Among the study population, the disease, test, and hospitalization episodes that had linked SARS-CoV-2 RT-PCR test results in the EHR data during the episode

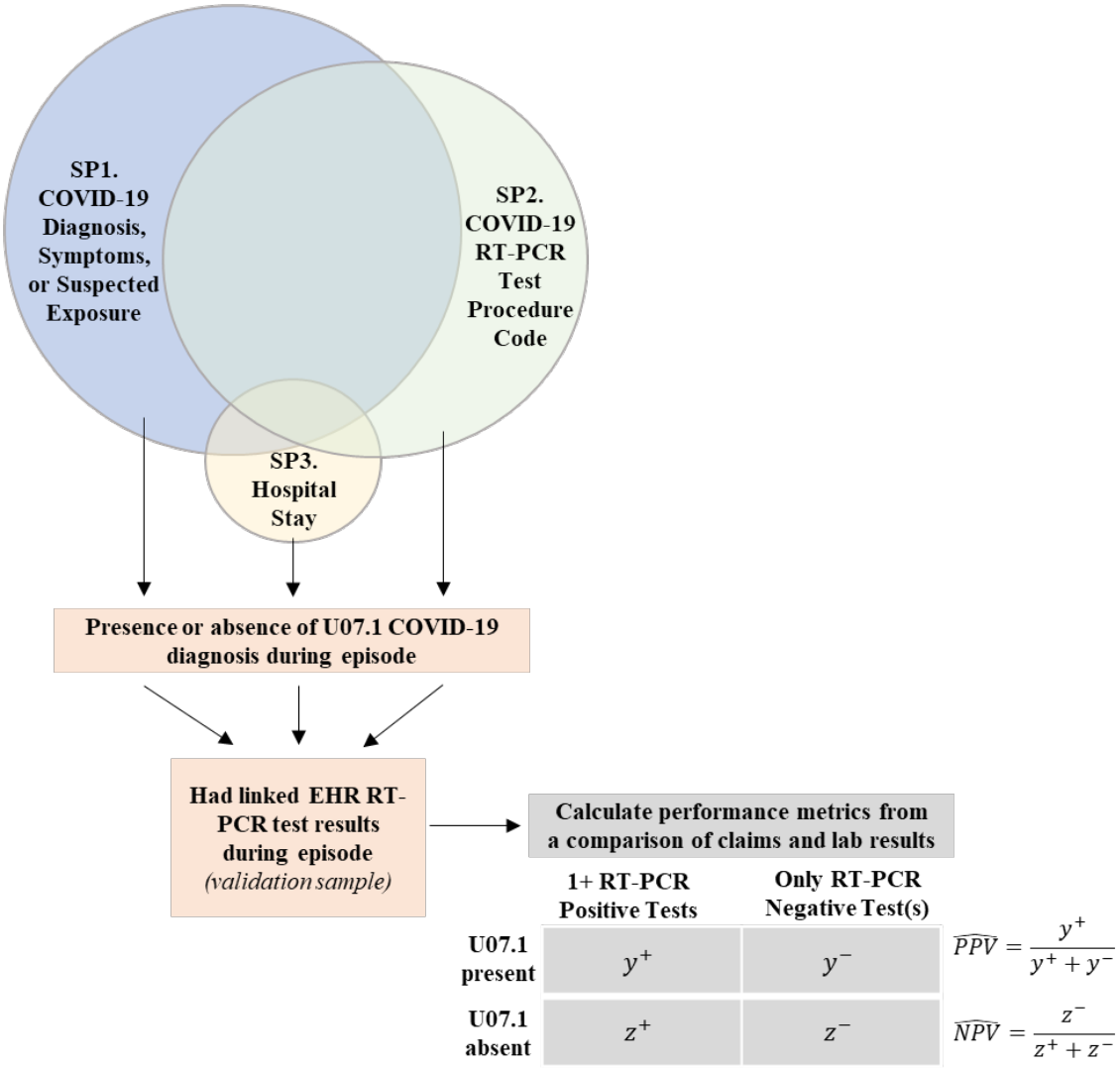
Episodes for each study population will be constructed using data from April 1, 2020, through the date for which claims data are at least 80% complete. Episodes will be anchored on the date of the index event, defined differently in the three study populations in the claims data. Episodes will subsequently be classified as positive or negative for COVID-19 based on the presence of U07.1 during the episode. Baseline information will be collected during the 6-month period prior to the start of the episode. Each episode is considered independent, and patients may have more than one episode. The unit of analysis is the episode.

In summary, episodes for each study population, which are further described in section C3, will be identified as follows:

- SP1a and SP1b:
    - SP1a: Disease episodes constructed using claims-based diagnoses indicating COVID-19 symptoms, a COVID-19 diagnosis, or suspected exposure to COVID-19, recorded during the study period
    - SP1b: Disease episodes constructed using claims-based diagnoses indicating a more limited symptom list for COVID-19-like illness (i.e., cough, fever, or shortness of breath), as defined by CDC COVIDView,[4] or a COVID-19 diagnosis recorded during the study period
- SP2: Test episodes constructed by identifying SARS-CoV-2 RT-PCR test procedures in claims data with a service date during the study period
- SP3: Hospitalization episodes with admission dates during the study period

A subset of disease episodes (SP1a and SP1b), test episodes (SP2), and hospitalization episodes (SP3) that have linked SARS-CoV-2 RT-PCR test results in EHRs during the episode will serve as the validation sample for each study population of interest. SARS-CoV-2 RT-PCR test results will be searched from the start of the episode through the end of the episode. The performance of the COVID-19 diagnosis code U07.1 will be evaluated in the validation samples by comparing it with the lab results. Figure 1 presents a conceptual flow diagram of the study population episodes of interest, the validation sample, and the study methods, which are described in the following sections.

Figure 1. Study overview*



Abbreviations: EHR, electronic health record; NPV, negative predictive value; PPV, positive predictive value; RT-PCR, reverse transcription polymerase chain reaction; SP, study population.

*SP1 (including SP1a and SP1b), SP2, and SP3 denote the three study populations. Episodes are defined in claims for SP1a, SP1b, SP2, and SP3. Patients can be included in more than one study population and can contribute to multiple episodes in the same population.

C3 Study Population

C3.1 Identify Disease, Test, and Hospitalization Episodes

Construct disease episodes based on diagnoses of COVID-19, COVID-19-related symptoms, or COVID-19 exposure for SP1a. In the claims portion of the claims-EHR linked data sources, diagnoses of COVID-19, COVID-19-related symptoms, and suspected COVID-19 exposure will be identified during the study period based on ICD-10-CM codes (see code list in the Appendix, section D1). Service dates when diagnoses were recorded will be used as diagnosis dates. The first diagnosis in any healthcare setting is defined as the index event, on which the disease episode will be anchored. Subsequent diagnoses will be grouped into the episode based on the diagnosis dates. Starting with the index event (i.e., first diagnosis), a subsequent diagnosis within 14 days of a prior diagnosis will be considered part of the same disease episode. The disease episode ends when there is a gap of more than 14 days between a diagnosis and any subsequent diagnoses. When an episode extends into a hospitalization, the episode will include the hospitalization from the admission date to the discharge date. After diagnoses of a single episode are grouped, the episode start and end dates will be assigned as follows:

- Episode start date = the date of the index event – 7 days
- Episode end date = the date of the last diagnosis + 7 days

Disease episodes group relevant diagnoses together and define a time period (from episode start date through episode end date) in which relevant RT-PCR test results will be identified. We selected 7 days prior to the date of the index event as the episode start date because SARS-CoV-2 RT-PCR tests conducted up to 7 days before the onset of symptoms may be informative for confirming a COVID-19 case, particularly if there is a delay in entering diagnoses on the clinical record after observing test results. We selected 7 days after the date of the last diagnosis to capture test results in the event that diagnoses were made before observing test results.

Construct disease episodes based on diagnoses of COVID-19 or CDC-defined COVID-19-like illness for SP1b. To identify the population SP1b, the same episode logic will be followed as specified for the population SP1a. However, the diagnoses will be limited to a subset of diagnoses included for SP1a. This subset comprises COVID-19 diagnoses and diagnoses of a CDC-defined subset of symptoms for COVID-19-like illnesses (i.e., cough, fever, or shortness of breath) identified by the "Symptom, Exposure Status, or Condition" values in the Appendix, section D1.

Construct test episodes based on procedures of SARS-CoV-2 RT-PCR tests for SP2. In the claims portion of the claims-EHR linked data sources, the Healthcare Common Procedure Coding System (HCPCS) codes for the SARS-CoV-2 RT-PCR test will be identified during the study period (see code list in the Appendix, section D2). Service dates when the RT-PCR procedures were performed will be used as test dates. The first test will be defined as the index event, on which the test episode will be anchored. Tests performed adjacent in time will be grouped together as test episodes. Starting with a

patient's index event (first test), a subsequent RT-PCR test within 21 days of a prior test will be considered part of the same test episode. The test episode ends when there is a gap of more than 21 days between a test and any subsequent tests. After tests of a single test episode are grouped, the episode start and end dates will be assigned as follows:

- Episode start date = the date of the index event – 7 days
- Episode end date = the date of the last test + 14 days

A test episode aims to delineate a period when a cluster of tests, where there are more than one for a patient, are likely related to one another to confirm a patient's case status. Multiple tests may be performed to further evaluate a patient with negative results (e.g., patients with recent exposure) or to confirm a positive result. The length of test episodes also defines the relevant period during which a COVID-19 diagnosis on claims will be identified and the EHR will be searched for SARS-CoV-2 RT-PCR test results. We selected 7 days prior to the date of the index event as the episode start date to capture COVID-19 diagnoses potentially made before observing test results. We selected 14 days after the date of the last COVID-19 test to allow sufficient time for test results to be returned and to capture diagnoses that were made after observing test results, which can take up to 14 days.

Construct hospitalization episodes for SP3. Acute inpatient stays with admission dates during the study period will be identified in the claims of the claims-EHR linked data. The admission of the first hospitalization will be defined as the index event. Consecutive hospitalizations with a subsequent admission date within 1 day of the prior discharge date (i.e., readmission on the same day or the next day of the prior discharge) will be considered transfers or readmissions. Consecutive hospitalizations will be connected to construct hospitalization episodes. The hospitalization episode start and end dates will be assigned as follows:

- Episode start date = the date of the index event – 14 days[a]
- Episode end date = the date of the last discharge

Disease, test, and hospitalization episodes defined above with continuous enrollment during the episodes and 6 months prior to the start of the episodes will be retained as the final study populations. Continuous enrollment is defined as patients' having continuous coverage of medical benefits, allowing for a coverage gap of up to 32 days.

C3.2 Classify COVID-19 Case Status of Disease Episodes, Test Episodes, and Hospitalizations

Disease, test, and hospitalization episodes meeting the continuous enrollment requirement will be classified into COVID-19-positive and COVID-19-negative episodes based on the presence or absence of COVID-19 diagnosis code U07.1 during the episodes. Episodes with at least one COVID-19 diagnosis code will be classified as

[a] This is consistent with CDC's COVID-NET definition, which tracks COVID-19 hospitalizations occurring within 14 days of a positive test. See https://www.cdc.gov/coronavirus/2019-ncov/covid-data/covid-net/purpose-methods.html.

COVID-19 positive. Episodes with no COVID-19 diagnosis code will be classified as COVID-19 negative. Diagnosis codes from all care settings will be used to classify episodes for SP1a, SP1b, and SP2. Discharge diagnoses from hospitalizations will be used to classify episodes for SP3.

C3.3 Select Validation Sample

Classified COVID-19-positive and COVID-19-negative episodes will be further examined to determine the presence of RT-PCR test results in the linked EHR data. SARS-CoV-2 RT-PCR test results will be identified based on Logical Observation Identifiers Names and Codes (LOINC) (Appendix, section D3) on the EHR, and the observation date associated with the LOINC will be used as the date of the test result. Episodes with at least one observed positive or negative or inconclusive RT-PCR test result in the EHR data during the episode will be selected. Four validation samples will be created, one for each study population.

C4 BEST Data Sources

This study will use linked claims-EHR sources from the Food and Drug Administration (FDA) Biologics Effectiveness and Safety (BEST) Initiative to identify the study population. For the generalizability assessment, the study will use the administrative claims data, i.e., the source data where the linked data originated. Table 1 outlines currently available data sources and the study period specific to each data source.

Table 1. Study Data Sources From FDA BEST Initiative

Data Source		Study Period	Population
Claims data sources *(for generalizability assessment)*	IBM MarketScan Commercial Database	April 1–August 31, 2020	Representative coverage; ~25 million on average annually
	OneFlorida Data Trust Florida Medicaid claims	April 1–August 31, 2020	Florida; ~3–4 million patients on average annually
	Optum Clinformatics Data Mart	April 1–September 30, 2020	National; ~14 million patients on average annually
Linked claims-EHR data sources *(for validation)*	IBM MarketScan Explorys Claims-EMR Data Set *(MarketScan commercial claims linked with Explorys EHR data)*	April 1–August 31, 2020	Linked EHR data from Explorys EHR Database has most coverage in OH, LA, and FL ~1–1.5 million patients on average annually
	OneFlorida Data Trust linked Medicaid-EHR	April 1–August 31, 2020	Florida; ~300–500 thousand patients on average annually
	OptumServe *(linked Clinformatics claims-OptumServe EHR data)*	April 1–September 30, 2020	Representative coverage; ~2 million patients on average annually

Abbreviations: BEST, Biologics Effectiveness and Safety; EHR, electronic health record; EMR, electronic medical record; FDA, Food and Drug Administration.

- ***IBM MarketScan Research Databases:*** The MarketScan Research Databases capture person-level clinical utilization, expenditures, and enrollment across inpatient, outpatient, prescription drug, and carve-out services. The data span over two decades since 1998 and come from a selection of large employers, health plans, and government and public organizations. The IBM MarketScan Commercial Database contains data from over 200 million active employees, early retirees, Consolidated Omnibus Budget Reconciliation Act (COBRA) continuees, and dependents insured by employer-sponsored plans in total.

- ***IBM MarketScan Explorys Claims-EMR Data Set (CED):*** CED consists of data that link the longitudinal treatment and economic claims records of patients from the MarketScan Commercial Database to the same patients' clinical records from the IBM Explorys EHR Database. The Explorys EHR Database comprises more than 30 health systems spanning academic centers and community practices. The EHRs available are limited to structured data elements that include diagnoses, procedures, immunizations, vital signs and biometrics, medical/surgical history, laboratory results, implantable devices, patient-reported outcomes, as well as inpatient drug administration and ambulatory prescriptions. The combined data set deterministically links patients in both the MarketScan and Explorys databases and provides administrative claims and rich clinical data to support epidemiologic analyses.
- ***OneFlorida Data Trust Florida Medicaid claims:*** The OneFlorida Data Trust contains claims data for Floridians enrolled in Medicaid, which is the source population used for the OneFlorida linked Medicaid-EHR population. The OneFlorida Data Trust provides Florida Medicaid data in the PCORnet common data model, which captures patient-level enrollment and clinical utilization across inpatient, outpatient, prescription drug, and other services for about 3–4 million annual enrollees.
- ***OneFlorida Data Trust linked Medicaid-EHR:*** The OneFlorida Data Trust is a repository of statewide healthcare data across Florida that is regularly refreshed. The Data Trust contains claims data for Floridians enrolled in Medicaid and robust patient-level EHR data from public and private healthcare systems, including diagnoses, procedures, medications, patient demographics, and unique patient identifiers. Patients are deterministically linked between claims and EHR records. Providers span from large integrated health delivery networks, 13 large hospitals, and ambulatory care and primary care facilities.
- ***OptumServe Clinformatics Data Mart:*** The OptumServe Clinformatics Data Mart contains longitudinal health information for commercially insured and Medicare Advantage enrollees, and it includes more than 66 million lives since 2007. The commercial portion of the Clinformatics Data Mart includes approximately 14.5 million people on an annual basis, and the median dwell time in the database for enrollees is approximately 2.5 years. The Optum

preadjudicated claims database contains preadjudicated claims for physician and hospital services and adjudicated claims for prescription drug services.

- ***OptumServe linked claims-EHR database:*** The OptumServe linked claims-EHR includes a total of approximately 25 million patients from 2007 to 2018, with approximately 2 million active annual enrollees. Optum's integrated claims-EHR database combines the adjudicated claims data with EHR data, including laboratory results.

C5 Analysis

C5.1 Performance Metrics

The following performance metrics will be calculated for each study population.

Positive predictive value (PPV). The PPV of the COVID-19 diagnosis code U07.1 is defined as the proportion of COVID-19-positive episodes that are confirmed by a positive SARS-CoV-2 RT-PCR test result.

PPV is calculated by (1) summing the number of claims-identified COVID-19-positive episodes in the validation sample that have at least one corresponding positive SARS-CoV-2 RT-PCR test result during the episode and (2) dividing that by the total number of claims-identified COVID-19-positive episodes in the validation sample. Note that if there are multiple RT-PCR tests during the episode, one positive test is sufficient to confirm a positive case.

Negative predictive value (NPV). The NPV of the COVID-19 diagnosis code U07.1 is defined as the proportion of COVID-19-negative episodes (i.e., the absence of a COVID-19 diagnosis during the episode) that are confirmed by negative SARS-CoV-2 RT-PCR test results during the episode. Note that if there are multiple RT-PCR tests during the episode, all must be negative to confirm a negative case.

NPV is calculated by (1) summing the number of claims-identified COVID-19-negative episodes in the validation sample with only negative SARS-CoV-2 RT-PCR test results during the episode and (2) dividing that by the total number of claims-identified COVID-19-negative episodes in the validation sample.

For conceptual clarity, as noted below and in Table 2, the PPV and NPV calculation directly excludes episodes with inconclusive lab results in the absence of any positive results from the denominator, leaving only episodes with definitive test results (true positive or true negative). Inconclusive test results are those that are not interpretable as positive or negative (e.g., results with entered values not classifiable as positive or negative).

$$\widehat{PPV} = \frac{y^+}{n^+_{test} - y^{\emptyset}} = \frac{y^+}{y^+ + y^-}$$

$$\widehat{NPV} = \frac{z^-}{n^-_{test} - z^{\emptyset}} = \frac{z^-}{z^+ + z^-}$$

Table 2. Calculation of Performance Metrics for COVID-19 Diagnosis Status

	SARS-CoV-2 RT-PCR Test Result			
Claims-Identified Outcome	**At Least One Positive Test in Episode**	**Only Negative Test in Episode**	**Any Inconclusive Results and No Positive Results in Episode**	**Row Total**
COVID-19 Diagnosis Code	y^+	y^-	$y^{\emptyset}$	n^+_{test}
No COVID-19 Diagnosis Code	z^+	z^-	$z^{\emptyset}$	n^-_{test}
Column Total	n^+_{ref}	n^-_{ref}	$n^{\emptyset}_{ref}$	n

Abbreviation: RT-PCR, reverse transcription polymerase chain reaction.

Note that for the performance metric calculations:

- $y^{\emptyset}$ and $z^{\emptyset}$ are the number of episodes classified as COVID-19 positive and COVID-19 negative, respectively, with inconclusive RT-PCR test results but no positive results in the linked EHR during the episodes.
- y^+ (true positive episode) is the number of claims-identified COVID-19-positive episodes with at least one positive SARS-CoV-2 RT-PCR test result in the linked EHR during the episodes.
- y^- (false positive episode) is the number of claims-identified COVID-19-positive episodes with only negative (and no positive) SARS-CoV-2 RT-PCR test results in the linked EHR during the episodes.
- z^+ (false negative episode) is the number claims-identified COVID-19-negative episodes that have at least one positive SARS-CoV-2 RT-PCR test result in the linked EHR during the episodes.
- z^- (true negative episode) is the number of claims-identified COVID-19-negative episodes that have only negative (no positive) SARS-CoV-2 RT-PCR test results in the linked EHR during the episodes.

C5.2 Confidence Intervals

We will calculate confidence intervals (CIs) for the performance metrics (PPV and NPV) using the Agresti-Coull interval (a slight modification of the better-known Wilson interval). Colloquially, this is called the "add two successes and two failures" rule; by this rule, the method addresses the CI's potential lack of coverage at the 0.05 nominal level for certain combinations of the metric and the binomial sample size.[5,6] Specifically, the Agresti-Coull interval is an adjustment to the standard Wald interval; at the nominal 0.05 level, the 95% CI is calculated as:

$$CI_{\widetilde{metric}} = \widetilde{metric} \pm 2\sqrt{\frac{\widetilde{metric}(1-\widetilde{metric})}{n_{\widetilde{metric}}}}$$

where $\widetilde{metric}$ and $n_{\widetilde{metric}}$ is defined per performance metric:

$\widetilde{PPV} = (y^+ + 2)/(y^+ + y^- + 4)$ and $\widetilde{n_{PPV}} = y^+ + y^- + 4$.

$\widetilde{NPV} = (z^- + 2)/(z^- + z^+ + 4)$ and $\widetilde{n_{NPV}} = z^- + z^+ + 4$.

C5.3 Stratifications and Subgroup of Interest

The performance metric estimates from each study population may differ by data source, care setting, calendar date, and population characteristics. If sample size permits, the performance metrics will be estimated in the strata of the following classifications in each data source:

1. Calendar month of the index event during the study period
2. Care settings at the index event (SP1a, SP1b, and SP2):
    - Inpatient (defined as admitted to a hospital with more than a 24-hour stay)
    - Outpatient (physician office, ambulatory clinic, or hospital outpatient settings)
    - Telemedicine (if available in the data source)
    - Long-term care (for data sources with sufficient representation of long-term care population)
    - Emergency department
3. Age group at the index event
    - Pediatrics (<18 years old)
    - Adults (≥18 years old and <65 years old)
    - Individuals ≥18 years old and <50 years old
    - Individuals ≥50 years old and <65 years old

Subgroup of pregnant women. The Center for Biologics Evaluation and Research (CBER) BEST Initiative has developed and validated a set of algorithms to identify gestational age and pregnancy outcomes with good to excellent performance among women aged 12–55 years at the time of the outcome.[7] The algorithms identify pregnancies by capturing pregnancy endpoints (full-term live births, preterm live births, spontaneous abortions, and stillbirths) using ICD-10-CM/Procedure Coding System (PCS) and other service codes (HCPCS and diagnosis-related group [DRG] codes) in women's claims. They then estimate a pregnancy start date and gestational age at the outcome using relevant ICD-10-CM/PCS and HCPCS codes on prenatal and delivery claims. The algorithms group obstetric services into pregnancy episodes based on hierarchical and spacing requirements. Evidence of high clinical accuracy for gestational age (such as the timing of assisted reproductive technology procedures and gestational

age determined during a first-trimester ultrasound) is prioritized when determining the pregnancy start date.

The pregnancy outcomes and estimated gestational age will be identified using ICD-10-CM/PCS, HCPCS, and DRG codes. The time period between the pregnancy start date and outcome date defines a pregnancy episode. A woman may have more than one pregnancy episode during the study period or within each calendar year. Disease, test, and hospitalization episodes will be classified to a pregnant subgroup if any portion of the episode overlaps with a woman's pregnancy episode. The performance metrics of the COVID-19 diagnosis will be assessed in the pregnant subpopulations of each study population. The disease, test, and hospitalization episodes overlapping with pregnancy may be further stratified by maternal age at delivery (12–19 years, 20–34 years, 35–44 years, 45–55 years), if sample size allows.

C5.4 Assess Generalizability of Estimated Performance Metrics

The performance of the COVID-19 diagnosis code U07.1 will be evaluated among episodes with SARS-CoV-2 RT-PCR test results. However, selection of the study population and the validation sample is likely not random. Whether the algorithm performance can be generalized to the source populations from which the study populations and validation samples are selected must be evaluated. Lack of representativeness may be introduced when we limit the study population to those patients with a linked EHR and then further when we select the validation samples by limiting to those episodes with RT-PCR test results during the episodes in the EHR.

Using the same methods described in section C3, four source populations will be identified in the claims databases (MarketScan, Florida Medicaid, and Optum Clinformatics) from which the linked claims-EHR episodes originate. The source populations will be respectively compared with the four study populations and the four validation samples, unless specified otherwise. The following characteristics will be evaluated to assess potential imbalance. We will calculate standardized mean differences (SMDs) to compare proportions and means between these groups. An absolute SMD value >0.20 will be used as the threshold to distinguish potentially meaningful differences between groups.

1. Presence of U07.1 code during the episodes
2. Presence of at least one RT-PCR procedure (HCPCS) on claims during the episodes (source populations/study populations/validation samples 1a and 1b)
3. Demographics at the time of the index event
    - Age at the start of the episode
    - Sex
    - Census region of patient residence (if available in the data source)
    - Patient residence of metropolitan versus nonmetropolitan area (if available in the data source)
    - Race/ethnicity (if available in the data source)

4. Clinical characteristics
    - Care setting at the index event (source populations/study populations/validation samples 1a, 1b, and 2)
    - Length of episode
    - Length of stay (source population/study population/validation sample 3)
    - Intensive care during hospitalization (source population/study population/validation sample 3)
    - Presence of COVID-19-related symptoms and potential exposure diagnoses listed in the Appendix, section D1, during the episodes
    - Comorbidities during the 6-month baseline period. Comorbidities will be defined by the ICD-10-CM-adapted Deyo-Charlson comorbidities.[8,9]
5. Healthcare utilization during the 6-month baseline period
    - Any hospitalizations
    - Any emergency department visit
    - Number of outpatient visits
    - Number of prescription fills

C5.5 Quantitative Bias Analysis

Among the validation sample, only the RT-PCR tests conducted by EHR networks contributing to CED, OneFlorida, or Optum EHR data will be captured. Patients may have additional tests conducted by providers or test sites outside of networks, and the test results are not accessible for analysis. Among the validation sample with an observed positive RT-PCR test result, misclassification is unlikely, because a single positive test is sufficient to confirm a true positive COVID-19 case. However, among the validation sample with only observed negative test results, a potential missed positive test would result in case misclassification.

The length of episodes in each study population includes a time period prior to the index event. This added lead time is expected to capture more positive RT-PCR test results to confirm a positive case. However, negative RT-PCR test results captured during this period may be less informative in that case status may change after the index event. The subset of the validation sample with *only* negative test results from the period prior to the index event date may be more susceptible to the misclassification mentioned above due to a potentially unobserved positive result. The study design assumes, provided no positive results are present, negative test results any time during the episodes are sufficient to confirm a COVID-19-negative episode. The impact of this potential misclassification will be assessed with a quantitative bias analysis (QBA). We will separately assume all and 50% of the validation sample in this subset received a positive test elsewhere. PPV and NPV under these two hypothetical scenarios will be computed and compared with the originally estimated PPV and NPV, respectively. The PPV from the QBA is expected to be higher than the originally estimated PPV, and the NPV from the QBA is expected to be lower than the originally estimated NPV.

C5.6 Sensitivity Analysis

Among the validation sample, some RT-PCR tests may have inconclusive results. Episodes with inconclusive test results but no positive results are excluded from the calculation of performance metrics (PPV and NPV). If more than 5% of the tests have inconclusive results, a sensitivity analysis will be conducted to assess the impact of the tests with inconclusive results. Two hypothetical and extreme scenarios will be presented in an effort to provide context for the range of performance metrics. In scenario 1, the performance metrics will be computed by assuming that all inconclusive results are positive. In scenario 2, the performance metrics will be computed by assuming that all inconclusive results are negative.

C6 Limitations

This study has several limitations.

First, the disease, test, and hospitalization episodes with SARS-CoV-2 RT-PCR test results may not be representative of episodes identified in the source population. Only patients present in both the source claims data and the EHR data may be linked and selected into the study population. Subsequently, only those with a SARS-CoV-2 RT-PCR test conducted within the facilities contributing to CED, OneFlorida, or Optum EHR data will be captured in the validation sample. Additionally, RT-PCR testing may not have been performed for all patients due to other factors such as test shortages (particularly during the early phase of the pandemic) and prioritization of immediate management of symptoms over testing. Comparability of the source population, study population, and validation sample will be evaluated as described in section C5.4.

Second, among the validation sample, patients may have additional tests conducted by providers or test sites outside of contributing EHR networks and therefore are not observed. This may affect performance estimates. For example, missing positive tests may potentially lead to overestimation of NPV (i.e., erroneously confirming COVID-19-negative episodes as true negatives) and underestimation of PPV (i.e., erroneously classifying COVID-19-positive episodes as false positives). The proposed QBA analysis (section C5.5) will inform the magnitude and direction this potential systematic error may introduce.

Third, RT-PCR test results in EHRs will be identified based on LOINC. The type/brand of test is not distinguishable; therefore, the sensitivity and specificity of the nucleic acid tests used as the reference method for this study are unknown. It has been reported that the sensitivity of different diagnostic tests may vary.[10,11] Additionally, the estimated performance metrics in this study will be based on data collected during the study period and thus may not reflect performance metrics across different time periods due to changing COVID-19 epidemiology curves and temporal changes in types of tests used with varying sensitivity and specificities.

Lastly, although the performance metrics estimated among a pregnancy subpopulation may be informative, the pregnancies identified in this study are limited to those with outcome dates within the study period, an estimated gestational age, and outcome types of live birth, spontaneous abortion, or stillbirth.

D Appendix

D1 COVID-19 Diagnosis, COVID-19-Related Symptoms, and Exposure Diagnosis Codes

Code	Code Description	Code Type	OMOP Concept ID	Symptom, Exposure Status, or Condition
R10.813	Right lower quadrant abdominal tenderness	ICD10CM	45544130	abdominal_pain
R10.30	Lower abdominal pain, unspecified	ICD10CM	45563290	abdominal_pain
R10.812	Left upper quadrant abdominal tenderness	ICD10CM	45534427	abdominal_pain
R10.816	Epigastric abdominal tenderness	ICD10CM	45534428	abdominal_pain
R10.827	Generalized rebound abdominal tenderness	ICD10CM	45548948	abdominal_pain
R10.32	Left lower quadrant pain	ICD10CM	45553715	abdominal_pain
R10.829	Rebound abdominal tenderness, unspecified site	ICD10CM	45553716	abdominal_pain
R10.13	Epigastric pain	ICD10CM	45558454	abdominal_pain
R10.11	Right upper quadrant pain	ICD10CM	45568112	abdominal_pain
R10.9	Unspecified abdominal pain	ICD10CM	45568114	abdominal_pain
R10.84	Generalized abdominal pain	ICD10CM	45558455	abdominal_pain
R10.31	Right lower quadrant pain	ICD10CM	45582694	abdominal_pain
R10.821	Right upper quadrant rebound abdominal tenderness	ICD10CM	45582695	abdominal_pain
R10.12	Left upper quadrant pain	ICD10CM	45597168	abdominal_pain
R10.824	Left lower quadrant rebound abdominal tenderness	ICD10CM	45602005	abdominal_pain
R10.826	Epigastric rebound abdominal tenderness	ICD10CM	45602006	abdominal_pain
R10.83	Colic	ICD10CM	45602007	abdominal_pain
R10.814	Left lower quadrant abdominal tenderness	ICD10CM	45606795	abdominal_pain
R10.33	Periumbilical pain	ICD10CM	45592407	abdominal_pain
R10.815	Periumbilic abdominal tenderness	ICD10CM	45602004	abdominal_pain
R10.822	Left upper quadrant rebound abdominal tenderness	ICD10CM	45597169	abdominal_pain
R10.823	Right lower quadrant rebound abdominal tenderness	ICD10CM	45597170	abdominal_pain
R10.811	Right upper quadrant abdominal tenderness	ICD10CM	45573009	abdominal_pain
R10.10	Upper abdominal pain, unspecified	ICD10CM	45577781	abdominal_pain
R10.817	Generalized abdominal tenderness	ICD10CM	45577782	abdominal_pain
R10.825	Periumbilic rebound abdominal tenderness	ICD10CM	45577783	abdominal_pain
R10.819	Abdominal tenderness, unspecified site	ICD10CM	45573010	abdominal_pain
R10.0	Acute abdomen	ICD10CM	35211289	abdominal_pain
R10.2	Pelvic and perineal pain	ICD10CM	35211290	abdominal_pain
R63.0	Anorexia	ICD10CM	35211405	anorexia
R07.1	Chest pain on breathing	ICD10CM	35211284	chest_pain
R07.89	Other chest pain	ICD10CM	45602002	chest_pain
R07.9	Chest pain, unspecified	ICD10CM	45534424	chest_pain
R07.81	Pleurodynia	ICD10CM	45587497	chest_pain
R07.82	Intercostal pain	ICD10CM	45597167	chest_pain

Code	Code Description	Code Type	OMOP Concept ID	Symptom, Exposure Status, or Condition
R68.83	Chills (without fever)	ICD10CM	45577807	chills
R05	Cough	ICD10CM	35211275	cough*
R19.7	Diarrhea, unspecified	ICD10CM	45534435	diarrhea
A08.39	Other viral enteritis	ICD10CM	45571414	diarrhea
A08.4	Viral intestinal infection, unspecified	ICD10CM	35205449	diarrhea
A09	Infectious gastroenteritis and colitis, unspecified	ICD10CM	35205450	diarrhea
R42	Dizziness and giddiness	ICD10CM	35211350	dizziness
R53.1	Weakness	ICD10CM	45602032	fatigue
R53.81	Other malaise	ICD10CM	45582718	fatigue
R53.83	Other fatigue	ICD10CM	45534458	fatigue
R53.82	Chronic fatigue, unspecified	ICD10CM	45573032	fatigue
R50.81	Fever presenting with conditions classified elsewhere	ICD10CM	45606818	fever*
R50.9	Fever, unspecified	ICD10CM	35211387	fever*
R50.82	Postprocedural fever	ICD10CM	45597189	fever*
R51	Headache	ICD10CM	35211388	headache
R43.0	Anosmia	ICD10CM	35211351	loss_of_smell_taste
R43.9	Unspecified disturbances of smell and taste	ICD10CM	45573025	loss_of_smell_taste
R43.1	Parosmia	ICD10CM	35211352	loss_of_smell_taste
R43.2	Parageusia	ICD10CM	35211353	loss_of_smell_taste
R43.8	Other disturbances of smell and taste	ICD10CM	35211354	loss_of_smell_taste
R65.10	Systemic inflammatory response syndrome (SIRS) of non-infectious origin without acute organ dysfunction	ICD10CM	45539355	multi_organ_failure
R65.11	Systemic inflammatory response syndrome (SIRS) of non-infectious origin with acute organ dysfunction	ICD10CM	45534462	multi_organ_failure
R65.20	Severe sepsis without septic shock	ICD10CM	45548977	multi_organ_failure
R65.21	Severe sepsis with septic shock	ICD10CM	45577803	multi_organ_failure
M79.10	Myalgia, unspecified site	ICD10CM	1595617	myalgia
M79.11	Myalgia of mastication muscle	ICD10CM	1595618	myalgia
M79.12	Myalgia of auxiliary muscles, head and neck	ICD10CM	1595619	myalgia
M79.18	Myalgia, other site	ICD10CM	1595620	myalgia
I40.0	Infective myocarditis	ICD10CM	35207750	myocarditis_pericarditis
I40.1	Isolated myocarditis	ICD10CM	35207751	myocarditis_pericarditis
I40.8	Other acute myocarditis	ICD10CM	35207752	myocarditis_pericarditis
I40.9	Acute myocarditis, unspecified	ICD10CM	35207753	myocarditis_pericarditis
I51.4	Myocarditis, unspecified	ICD10CM	35207798	myocarditis_pericarditis
J10.82	Influenza due to other identified influenza virus with myocarditis	ICD10CM	45591546	myocarditis_pericarditis
J11.82	Influenza due to unidentified influenza virus with myocarditis	ICD10CM	45543255	myocarditis_pericarditis
B33.22	Viral myocarditis	ICD10CM	45581156	myocarditis_pericarditis
B33.23	Viral pericarditis	ICD10CM	45571465	myocarditis_pericarditis

Code	Code Description	Code Type	OMOP Concept ID	Symptom, Exposure Status, or Condition
I30.0	Acute nonspecific idiopathic pericarditis	ICD10CM	35207715	myocarditis_pericarditis
I30.1	Infective pericarditis	ICD10CM	35207716	myocarditis_pericarditis
I30.8	Other forms of acute pericarditis	ICD10CM	35207717	myocarditis_pericarditis
I30.9	Acute pericarditis, unspecified	ICD10CM	35207718	myocarditis_pericarditis
I32	Pericarditis in diseases classified elsewhere	ICD10CM	35207725	myocarditis_pericarditis
I41	Myocarditis in diseases classified elsewhere	ICD10CM	35207754	myocarditis_pericarditis
I31.0	Chronic adhesive pericarditis	ICD10CM	35207719	myocarditis_pericarditis
I31.1	Chronic constrictive pericarditis	ICD10CM	35207720	myocarditis_pericarditis
R11.0	Nausea	ICD10CM	45534429	nausea_vomiting
R11.10	Vomiting, unspecified	ICD10CM	45602008	nausea_vomiting
R11.11	Vomiting without nausea	ICD10CM	45573011	nausea_vomiting
R11.12	Projectile vomiting	ICD10CM	45558456	nausea_vomiting
R11.13	Vomiting of fecal matter	ICD10CM	45573012	nausea_vomiting
R11.14	Bilious vomiting	ICD10CM	45568115	nausea_vomiting
R11.15	Cyclical vomiting syndrome unrelated to migraine	ICD10CM	1553844	nausea_vomiting
R11.2	Nausea with vomiting, unspecified	ICD10CM	45606796	nausea_vomiting
R11.3	Other vomiting without nausea	ICD10CM	35211291	nausea_vomiting
R00.2	Palpitations	ICD10CM	35211263	palpitations
R00.8	Other abnormalities of heart beat	ICD10CM	35211264	palpitations
R00.9	Unspecified abnormalities of heart beat	ICD10CM	45577776	palpitations
J95.821	Acute postprocedural respiratory failure	ICD10CM	45538487	respiratory_failure
J95.822	Acute and chronic postprocedural respiratory failure	ICD10CM	45562471	respiratory_failure
J96.92	Respiratory failure, unspecified with hypercapnia	ICD10CM	45533563	respiratory_failure
J96.21	Acute and chronic respiratory failure with hypoxia	ICD10CM	45543283	respiratory_failure
J96.11	Chronic respiratory failure with hypoxia	ICD10CM	45538489	respiratory_failure
J96.00	Acute respiratory failure, unspecified whether with hypoxia or hypercapnia	ICD10CM	45605906	respiratory_failure
J96.10	Chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	ICD10CM	45548131	respiratory_failure
J96.01	Acute respiratory failure with hypoxia	ICD10CM	45567283	respiratory_failure
J96.90	Respiratory failure, unspecified, unspecified whether with hypoxia or hypercapnia	ICD10CM	45567284	respiratory_failure
J96.22	Acute and chronic respiratory failure with hypercapnia	ICD10CM	45581868	respiratory_failure
J96.91	Respiratory failure, unspecified with hypoxia	ICD10CM	45605907	respiratory_failure
J96.12	Chronic respiratory failure with hypercapnia	ICD10CM	45572177	respiratory_failure
J96.02	Acute respiratory failure with hypercapnia	ICD10CM	45596289	respiratory_failure
J96.20	Acute and chronic respiratory failure, unspecified whether with hypoxia or hypercapnia	ICD10CM	45596290	respiratory_failure
P28.5	Respiratory failure of newborn	ICD10CM	35210515	respiratory_failure
R09.2	Respiratory arrest	ICD10CM	35211287	respiratory_failure
R06.09	Other forms of dyspnea	ICD10CM	45548944	shortness_of_breath*
R06.00	Dyspnea, unspecified	ICD10CM	45587496	shortness_of_breath*

Code	Code Description	Code Type	OMOP Concept ID	Symptom, Exposure Status, or Condition
R06.01	Orthopnea	ICD10CM	45597165	shortness_of_breath*
R06.02	Shortness of breath	ICD10CM	45534422	shortness_of_breath*
R06.03	Acute respiratory distress	ICD10CM	1326788	shortness_of_breath*
R06.1	Stridor	ICD10CM	35211276	shortness_of_breath*
R06.2	Wheezing	ICD10CM	35211277	shortness_of_breath*
R06.4	Hyperventilation	ICD10CM	35211279	shortness_of_breath*
R06.5	Mouth breathing	ICD10CM	35211280	shortness_of_breath*
R06.82	Tachypnea, not elsewhere classified	ICD10CM	45539314	shortness_of_breath*
J02.8	Acute pharyngitis due to other specified organisms	ICD10CM	35207923	sore_throat
J02.9	Acute pharyngitis, unspecified	ICD10CM	35207924	sore_throat
U07.1	COVID-19, virus identified	ICD10CM	702953	COVID-19*
Z03.818	Encounter for observation for suspected exposure to other biological agents ruled out	ICD10CM	45552061	COVID-19_exposure
Z20.828	Contact with and (suspected) exposure to other viral communicable diseases	ICD10CM	45542411	COVID-19_exposure
Z11.59	Encounter for screening for other viral diseases	ICD10CM	45595484	COVID-19_exposure

Abbreviations: ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; OMOP, Observational Medical Outcomes Partnership.

*Denotes diagnoses that are included in the CDC COVID-like illness definition used in study population 1b.

D2 SARS-CoV-2 RT-PCR Test HCPCS/CPT Codes

HCPCS/CPT	Description
87635	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) Coronavirus disease [COVID-19]), amplified probe technique
U0001	CDC testing laboratories to test patients for SARS-CoV-2
U0002	Non-CDC laboratory tests for SARS-CoV-2/2019-nCoV (COVID-19)
U0003	Infectious agent detection by nucleic acid (DNA or RNA); severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (Coronavirus disease [COVID-19]), amplified probe technique
U0004	2019-nCoV Coronavirus, SARS-CoV-2/2019-nCoV (COVID-19), any technique, multiple types or subtypes (includes all targets), non-CDC
0202U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab
0223U	Infectious disease (bacterial or viral respiratory tract infection), pathogen-specific nucleic acid (DNA or RNA), 22 targets including severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), qualitative RT-PCR, nasopharyngeal swab

Abbreviations: CDC, Centers for Diseases Control and Prevention; CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; RT-PCR, reverse transcription polymerase chain reaction.

D3 SARS-CoV-2 RT-PCR Test LOINC[b]

LOINC	Long Common Name
94745-7	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Respiratory specimen by NAA with probe detection
94746-5	SARS-CoV-2 (COVID-19) RNA [Cycle Threshold #] in Unspecified specimen by NAA with probe detection
94819-0	SARS-CoV-2 (COVID-19) RNA [Log #/volume] (viral load) in Unspecified specimen by NAA with probe detection
94565-9	SARS coronavirus 2 RNA [Presence] in Nasopharynx by NAA with non-probe detection
94759-8	SARS-CoV-2 (COVID-19) RNA [Presence] in Nasopharynx by NAA with probe detection
94500-6	SARS coronavirus 2 RNA [Presence] in Respiratory specimen by NAA with probe detection
94845-5	SARS-CoV-2 (COVID-19) RNA [Presence] in Saliva (oral fluid) by NAA with probe detection
94660-8	SARS-CoV-2 (COVID-19) RNA [Presence] in Serum or Plasma by NAA with probe detection
94309-2	SARS Coronavirus 2 RNA [Presence] in Unspecified specimen Qualitative by NAA with probe detection
41458-1	SARS coronavirus RNA [Presence] in Unspecified specimen by NAA with probe detection
94534-5	SARS coronavirus 2 RdRp gene [Presence] in Respiratory specimen by NAA with probe detection
95608-6	SARS-CoV-2 (COVID-19) RNA [Presence] in Respiratory specimen by NAA with non-probe detection
94533-7	SARS-CoV-2 (COVID19) N gene [Presence] in Respiratory specimen by NAA with probe detection
94640-0	SARS coronavirus 2 S gene [Presence] in Respiratory specimen by NAA with probe detection
94559-2	SARS coronavirus 2 ORF1ab region [Presence] in Respiratory specimen by NAA with probe detection
94502-2	SARS-related coronavirus RNA [Presence] in Respiratory specimen by NAA with probe detection
95423-0	Influenza virus A + B and SARS-CoV-2 (COVID-19) identified in Respiratory specimen by NAA with probe detection
95409-9	SARS coronavirus 2 (COVID19) N gene [Presence] in Nose by NAA with probe detection
95425-5	SARS-CoV-2 (COVID-19) N gene [Presence] in Saliva (oral fluid) by NAA with probe detection
94760-6	SARS coronavirus 2 N gene [Presence] in Nasopharynx by NAA with probe detection
95406-5	SARS-CoV-2 (COVID19) RNA [Presence] in Nose by NAA with probe detection
94758-0	SARS-related coronavirus E gene [Presence] in Respiratory specimen by NAA with probe detection
96091-4	SARS-CoV-2 (COVID-19) RdRp gene [Presence] in Saliva (oral fluid) by NAA with probe detection
94316-7	SARS-CoV-2 (COVID-19) N gene [Presence] in Specimen by NAA with probe detection

Abbreviations: LOINC, Logical Observation Identifiers Names and Codes; NAA, nucleic acid amplification.

[b] Source: Centers for Diseases Control and Prevention. LOINC In Vitro Diagnostic (LIVD) Test Code Mapping for SARS-CoV-2 Tests. (Accessed April 1, 2021, at https://www.cdc.gov/csels/dls/sars-cov-2-livd-codes.html.)

D4 Abbreviations

BEST: Biologics Effectiveness and Safety

CBER: Center for Biologics Evaluation and Research

CDC: Centers for Disease Control and Prevention

CED: IBM MarketScan Explorys Claims-EMR Data Set

CI: confidence interval

COVID-19: coronavirus disease 2019

CPT: Current Procedural Terminology

DRG: diagnosis-related group

EHR: electronic health record

EMR: electronic medical record

FDA: Food and Drug Administration

HCPCS: Healthcare Common Procedure Coding System

ICD-10-CM/PCS: International Classification of Diseases, Tenth Revision, Clinical Modification/Procedure Coding System

LOINC: Logical Observation Identifiers Names and Codes

NAAT: nucleic acid amplification test

NPV: negative predictive value

PPV: positive predictive value

QBA: quantitative bias analysis

RT-PCR: reverse transcriptase polymerase chain reaction

SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

SMD: standardized mean difference

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