Natural History of Coagulopathy in Patients with COVID-19 in a Real-World Electronic Health Data Network

ISPE COVID-19 Session

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- No external funding to disclose

- The views expressed in this presentation are those of the presenter and do not necessarily reflect those of the FDA

Background

- COVID-19 infection may predispose patients to both venous and arterial thrombotic events

- Previously published observational studies reported incidence of venous thromboembolic complications ranging between 3-35% in COVID-19 patients[1,2,3]

[1]Levi M, Thachil J, Iba T, Levy JH. Coagulation abnormalities and thrombosis in patients with COVID-19, *Lancet*. 2020 Jun; 7(6), e438-e440.
[2]Bompard F, Monnier H, Saab I, et al. Pulmonary embolism in patients with Covid-19 pneumonia. *European Respiratory Journal*. 2020 Jul; 56(1), 2001365.
[3]Moores LK, Tritschler T, Brosnahan S, et al. Prevention, diagnosis and treatment of venous thromboembolism in patients with COVID-19: CHEST Guideline and Expert Panel Report, *Chest*. 2020; 158(3): 1143-1163.

Objective

- To evaluate the feasibility of using real-world Electronic Health Record (EHR) data to determine the prevalence of thrombotic-related outcomes, COVID-severity-related outcomes, medication utilization, and availability of laboratory measures among COVID-19 positive hospitalized patients

TriNetX – Distributed Research Network
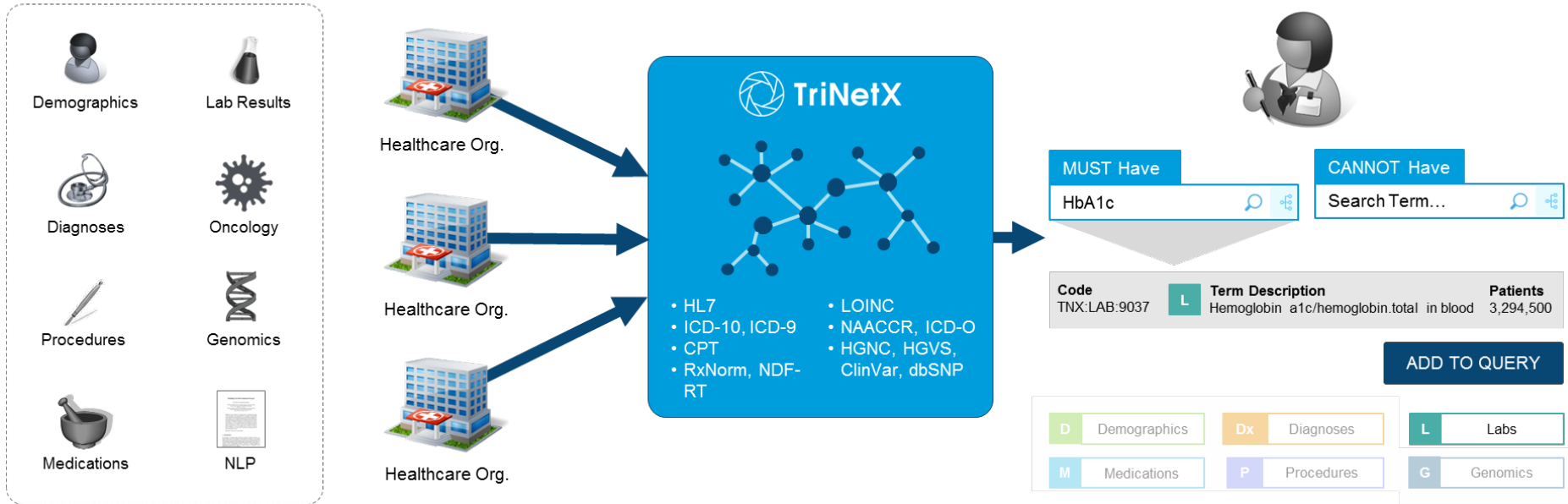
REAL WORLD DATA
Real-time access to patient populations, driven and refreshed by electronic medical record (EMR) data

USA NETWORK
- Includes 90M patients from 67 Healthcare Organizations (HCOs) in 27 States
- Academic and community health systems
- Primary through tertiary care for adults and children

INTERACTIVE QUERYING PLATFORM
- Common terminology used for mapping
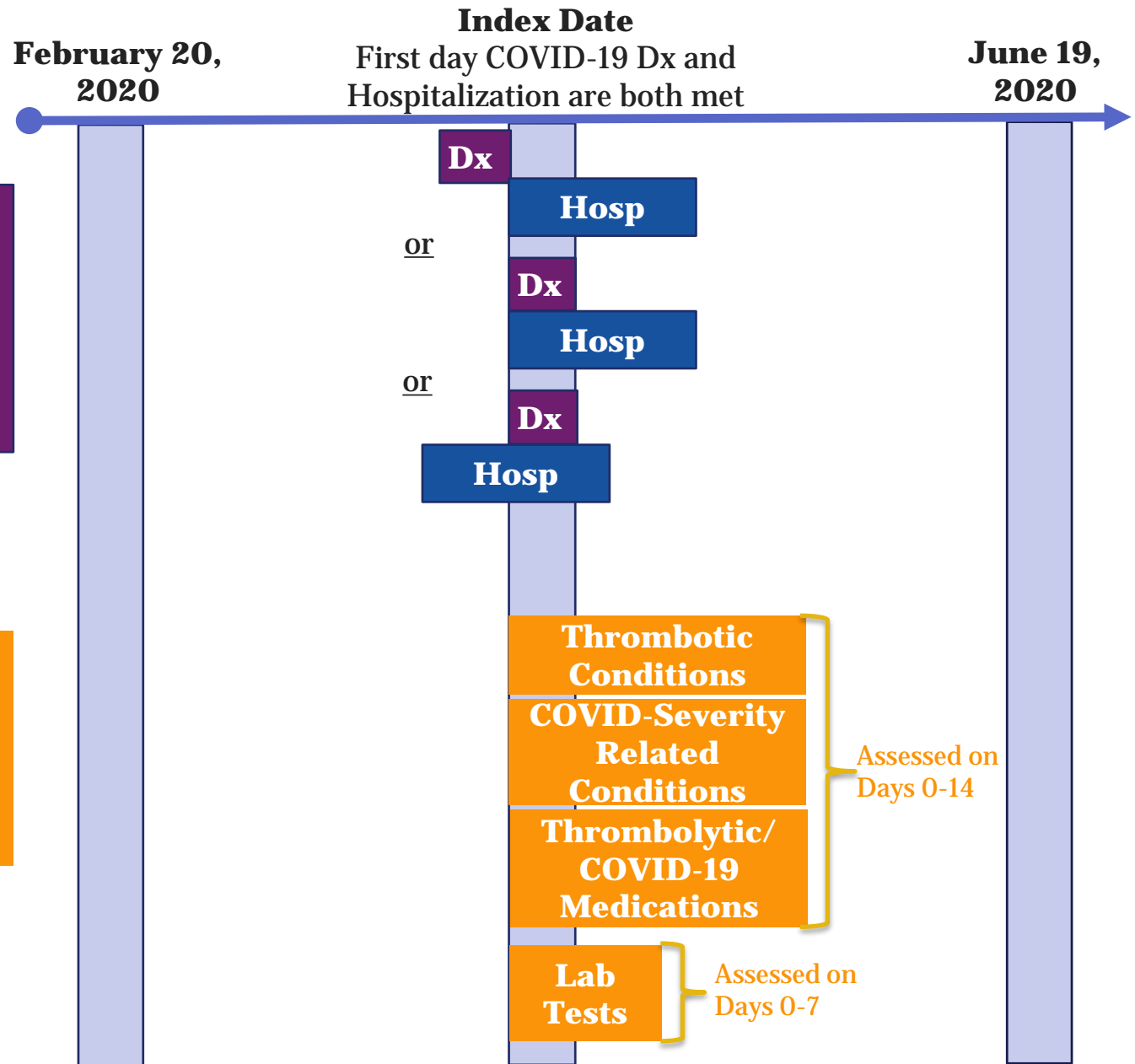- Enables rapid querying and real-world evidence generation

Demographics   Lab Results

Diagnoses   Oncology

Procedures   Genomics

Medications   NLP

Healthcare Org.

Healthcare Org.

Healthcare Org.

TriNetX

- HL7
- ICD-10, ICD-9
- CPT
- RxNorm, NDF-RT
- LOINC
- NAACCR, ICD-O
- HGNC, HGVS, ClinVar, dbSNP

MUST Have
HbA1c

CANNOT Have
Search Term...

Code		Term Description	Patients
TNX:LAB:9037	L	Hemoglobin a1c/hemoglobin.total in blood	3,294,500

ADD TO QUERY

D	Demographics	Dx	Diagnoses	L	Labs
M	Medications	P	Procedures	G	Genomics

Methods to define diagnoses and outcomes

Definition	Method	Examples*
COVID-19 Status		
Diagnosis, or	ICD-10 diagnosis codes	U07.1, B34.2, B97.2, J12.81
Antigen or RNA Testing	LOINC	94309-2, 94500-6, 94533-7
Thrombotic Events	ICD-10, CPT, HCPCS codes	I26 (PE), I21 (MI), I20 (Angina)
Severity Outcomes	ICD-10, CPT, HCPCS codes	J18 (Pneumonia), 1014859 (Mech Vent)
Medications	RxNorm, HCPCS codes	67108 (LMWH), 18631 (azithromycin)
Laboratory measures	LOINC	718-7 (Hemoglobin)

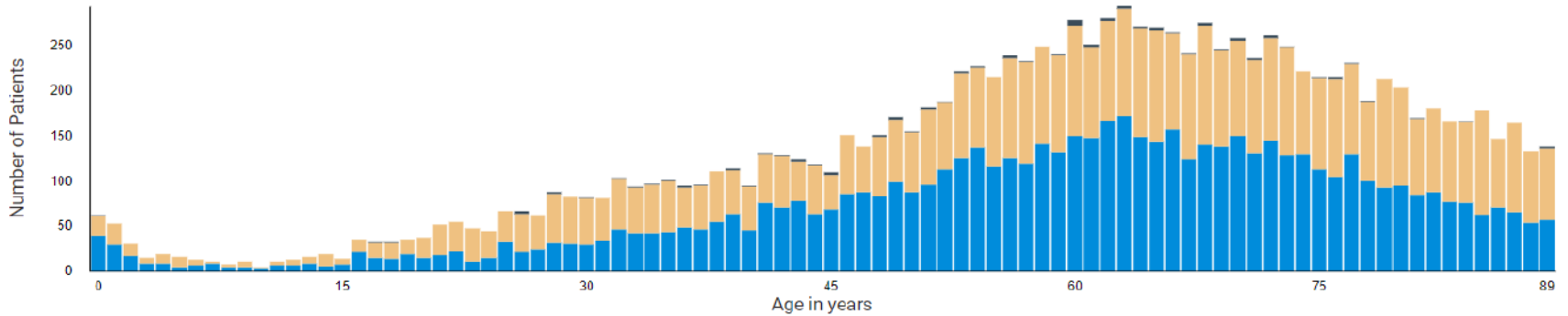* These are a small number of examples; many more codes were used in our analysis

Study Design

February 20, 2020

Index Date
First day COVID-19 Dx and Hospitalization are both met

June 19, 2020

Case Identification Criteria

Dx: ICD-10 Dx code or COVID-19 Antigen/RNA test

Hosp: Hospitalization within 1-week of Dx

Dx

Hosp

or

Dx

Hosp

or

Dx

Hosp

Case Characteristics

Thrombotic Conditions

COVID-Severity Related Conditions

Thrombolytic/ COVID-19 Medications

Assessed on Days 0-14

Lab Tests

Assessed on Days 0-7

Possible scenarios that may impact capture of outcomes/medications/labs

Day 0
(First evidence of
COVID diagnosis
and hospitalized)

Day 14

Captured in TriNetX

Not captured in TriNetX
(and not reported to the system)

Patient A

Study outcome

Patient B

Study outcome out of
the system and not
captured

Patient C

Study outcome out of the
system and not captured

Study outcome
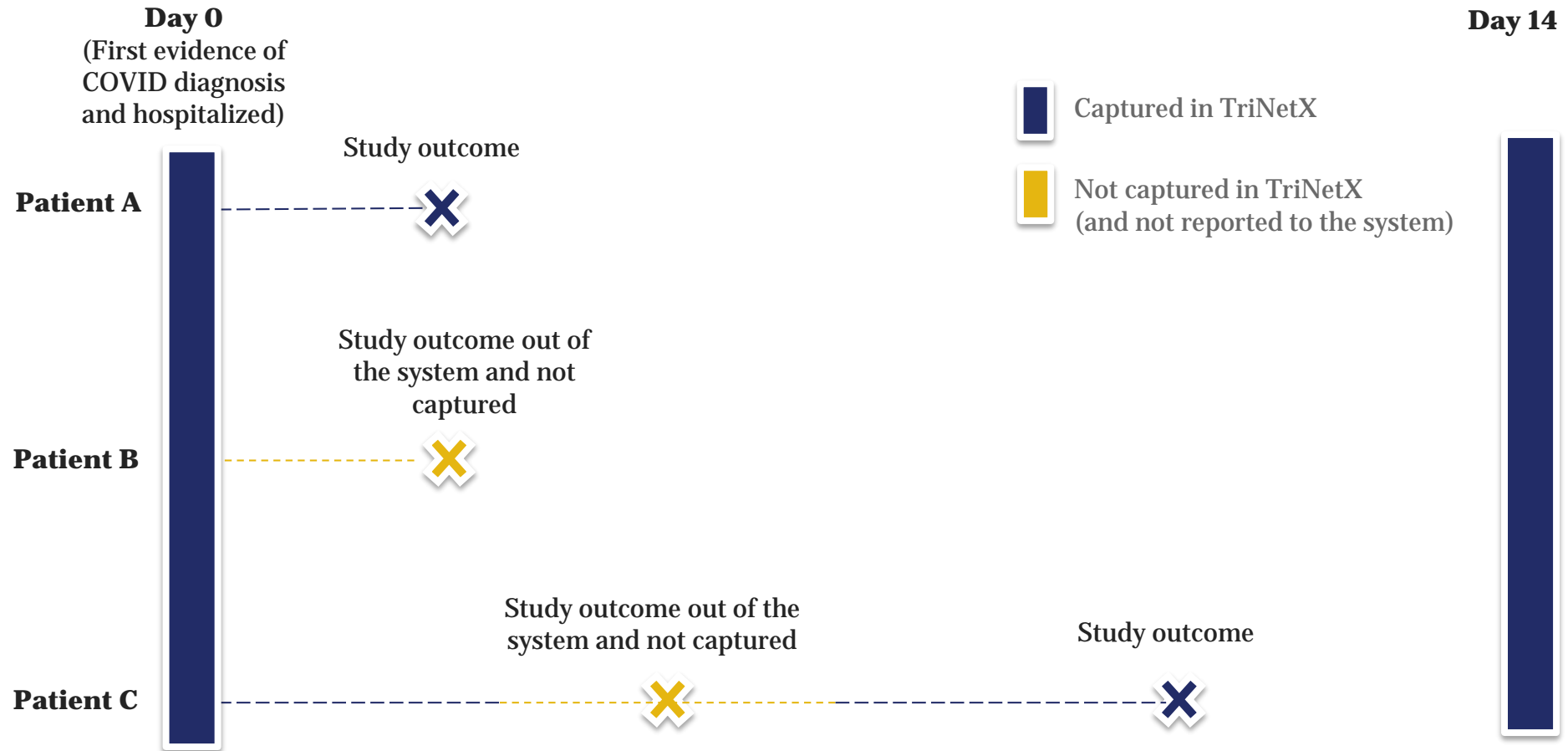
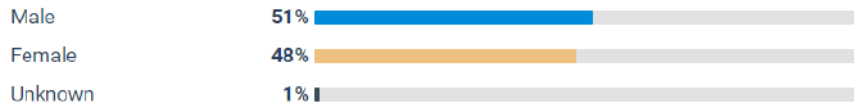# COVID-19 Patient Demographics

Patients 90 and Older: 551

	Total Patients	Minimum Age	Maximum Age	Mean Age	Standard Deviation
	12,560	0	90	60	20

Sex

Male	51%	
Female	48%	
Unknown	1%	

Ethnicity

Not Hispanic or Latino	52%	
Unknown Ethnicity	36%	
Hispanic or Latino	12%	

Race

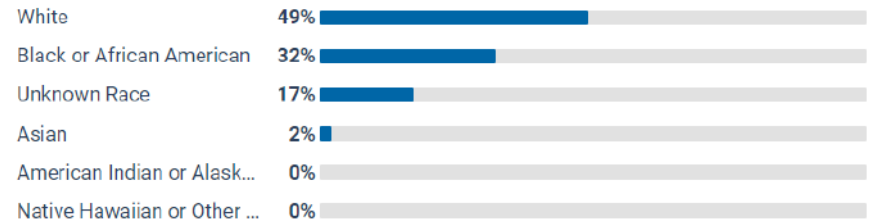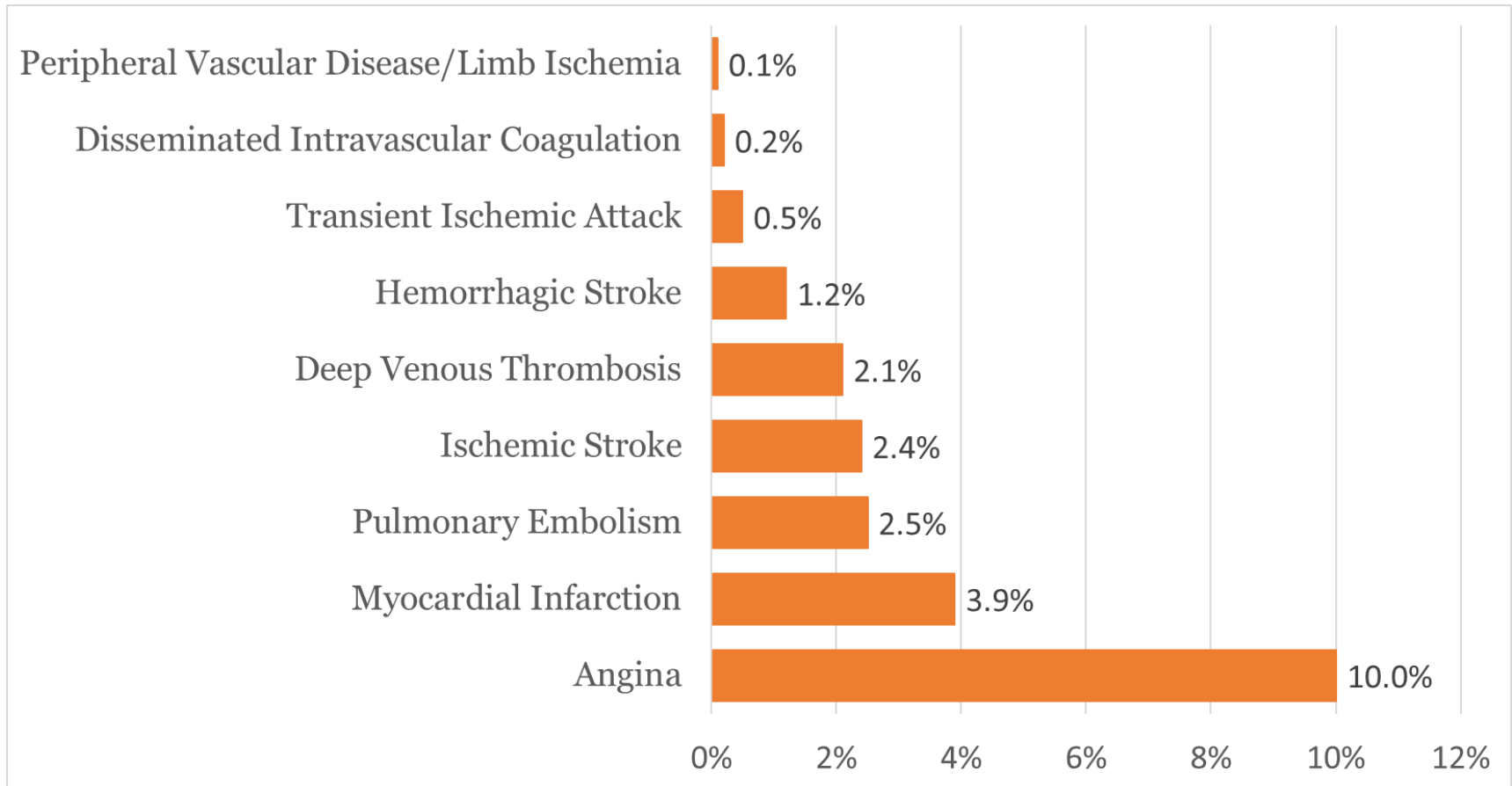|		
White	49%	
Black or African American	32%	
Unknown Race	17%	
Asian	2%	
American Indian or Alask...	0%	
Native Hawaiian or Other ...	0%	

Screenshot from TriNetX Platform

Prevalence of Thrombotic-Related Outcomes
within 2 Weeks on or after Hospitalization with COVID-19

Outcome	Percentage
Peripheral Vascular Disease/Limb Ischemia	0.1%
Disseminated Intravascular Coagulation	0.2%
Transient Ischemic Attack	0.5%
Hemorrhagic Stroke	1.2%
Deep Venous Thrombosis	2.1%
Ischemic Stroke	2.4%
Pulmonary Embolism	2.5%
Myocardial Infarction	3.9%
Angina	10.0%

Prevalence of COVID-Severity Related Outcomes
within 2 Weeks on or after Hospitalization with COVID-19

Outcome	Prevalence
ECMO	0.5%
Supplemental Oxygen (Diagnostic Terms)	3.6%
Supplemental Oxygen (Procedural Terms)	9.8%
ARDS	12.2%
Mechanical Ventilation	15.6%
Hypoxemia	19.8%
Sepsis	22.3%
Acute Respiratory Failure	42.0%
Pneumonia	52.0%
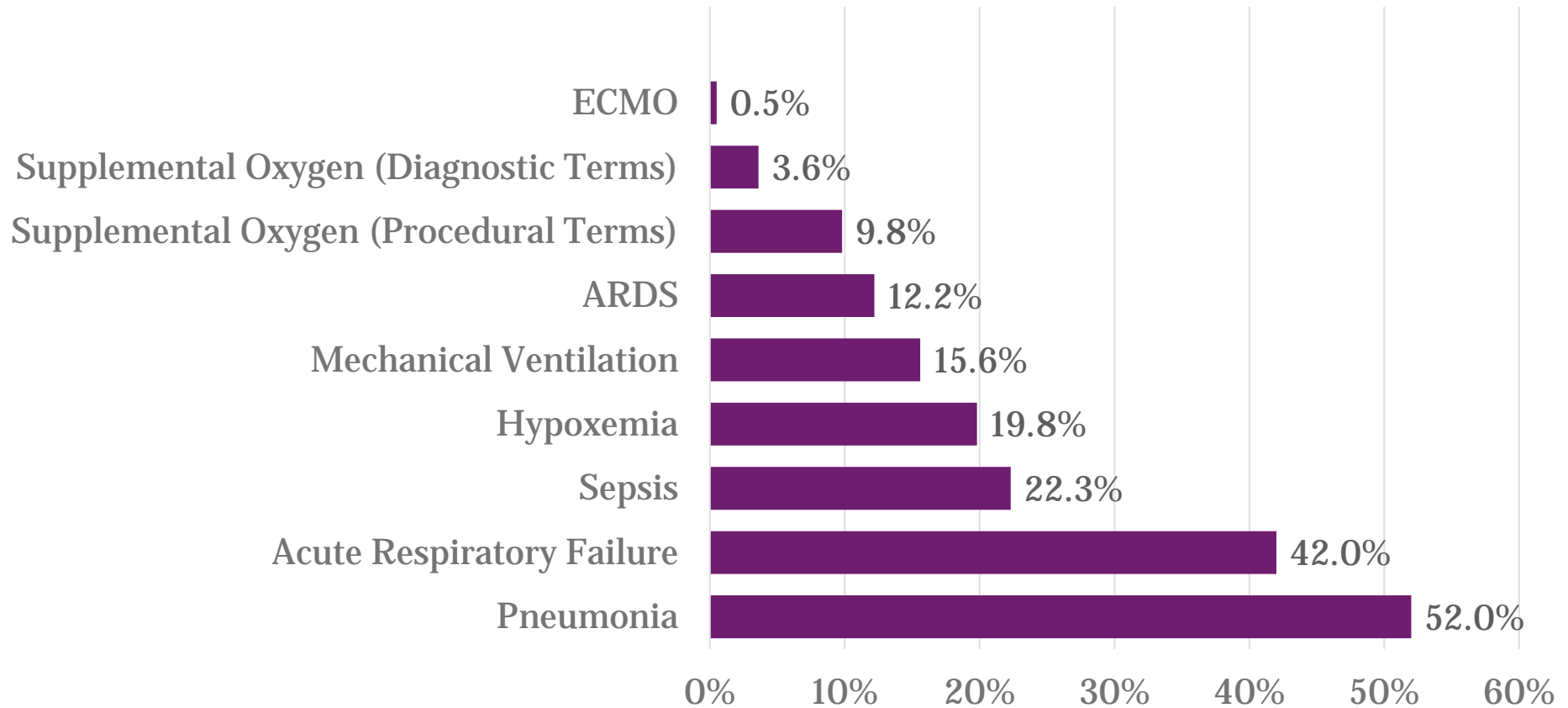
Prevalence of Medication Utilization
within 2 Weeks on or after Hospitalization with COVID-19

Medication	Prevalence
Dexamethasone	3.3%
Norepinephrine	4.6%
Factor Xa Inhibitors	8.8%
Hydroxychloroquine or Chloroquine	18.6%
Anti-Platelet Therapy	18.7%
Heparin	20.1%
Azithromycin	22.7%
Low Molecular Weight Heparin	36.1%
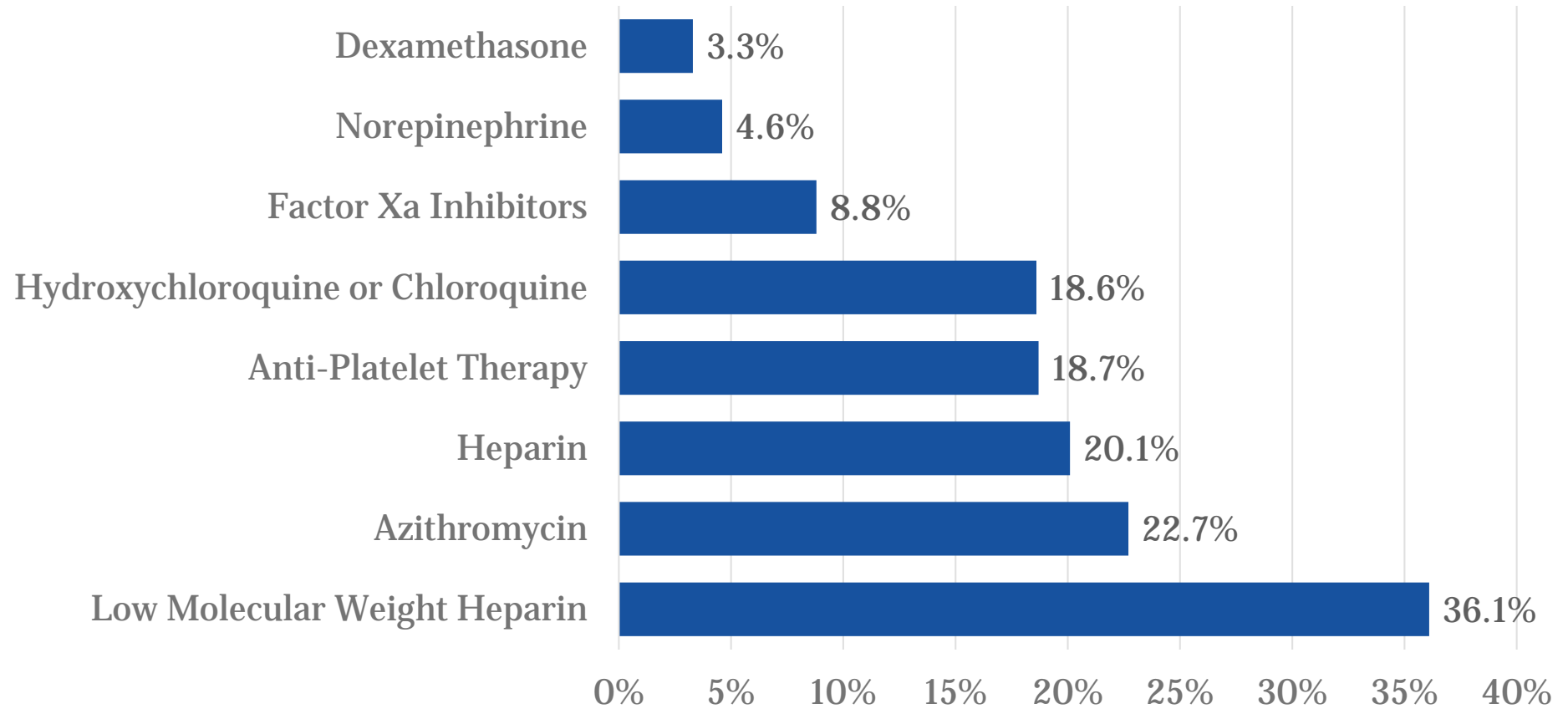
Laboratory Measures Evaluation
within 1 Week on or after Hospitalization with COVID-19

	N	%	Mean	SD
Total COVID-19 Patients	12,560	100.0%	--	--
Hemoglobin	11,410	90.8%	11.2 g/dL	2.3
Platelet Count	10,850	86.4%	252.8 10^3 cells/µL	124.4
White Blood Cell Count	9,840	78.3%	8.5 10^3 cells/µL	5.5
C-Reactive Protein	8,160	65.0%	72.8 mg/L	88.9
Prothrombin Time (PT)	4,940	39.3%	14.3 s	6.0
Partial Thromboplastin Time (PTT)	4,680	37.3%	34.7 s	16.0
Troponin	3,240	25.8%	5.4 ng/mL	39.3
D-Dimer (FEU)	3,200	25.5%	296.8 ng/mL FEU	1160.0
D-Dimer (DDU)	2,250	17.9%	855.9 µg/dL DDU	1858.8

Limitations

- Electronic health records lack longitudinal data
  - information recorded outside of the network HCOs is not available
  - unable to determine if absence of data is meaningful or if the data are missing
    - unlike longitudinal claims data that have been adjudicated for reimbursement

- We could not view date-stamps for data within a single healthcare encounter for individual patients in the application
  - temporality of treatment and outcome cannot be assessed

- Admission and discharge dates are not always recorded for patients on the USA Network
  - to capture hospitalized COVID-19 patients, we required occurrence of hospitalization within a given time window relative to COVID-19 diagnosis

Summary

- We identified just over 12,500 hospitalized COVID-19 patients in the USA network in mid-June

  - We reported the prevalence of thrombotic-related outcomes, COVID-19-severity-related outcomes, and medication utilization and found:

    - 2.5 % had a pulmonary embolism and 2.1% had a deep venous thrombosis
    - 52.0% had pneumonia and 42.0% had acute respiratory failure
    - 36.1% used low molecular weight heparin and 20.1% used heparin

  - We determined that most patients had common lab procedures resulted within 1 week of COVID-19 diagnosis and hospitalization

Next Steps

- Further work to explore the natural history of coagulopathy - including the epidemiology of arterial and venous thrombotic events - among COVID-19 patients in the inpatient setting is underway[1]

[1]https://www.sentinelinitiative.org/methods-data-tools/methods/descriptive-assessment-natural-history-coagulopathy-covid-19

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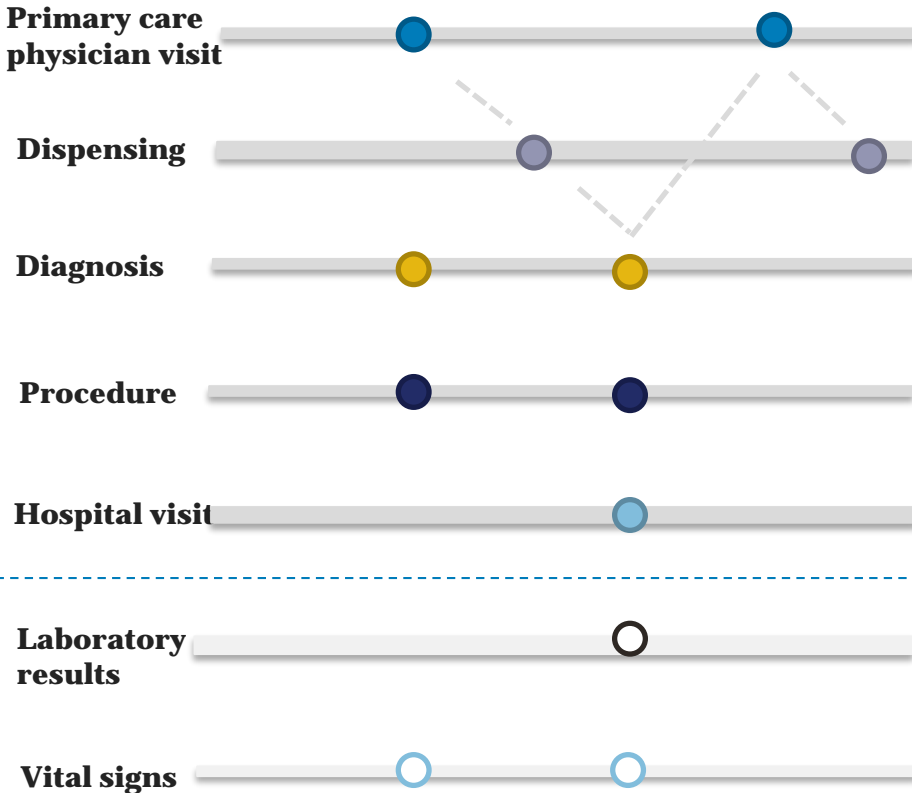
Thank You

Supplemental Slides
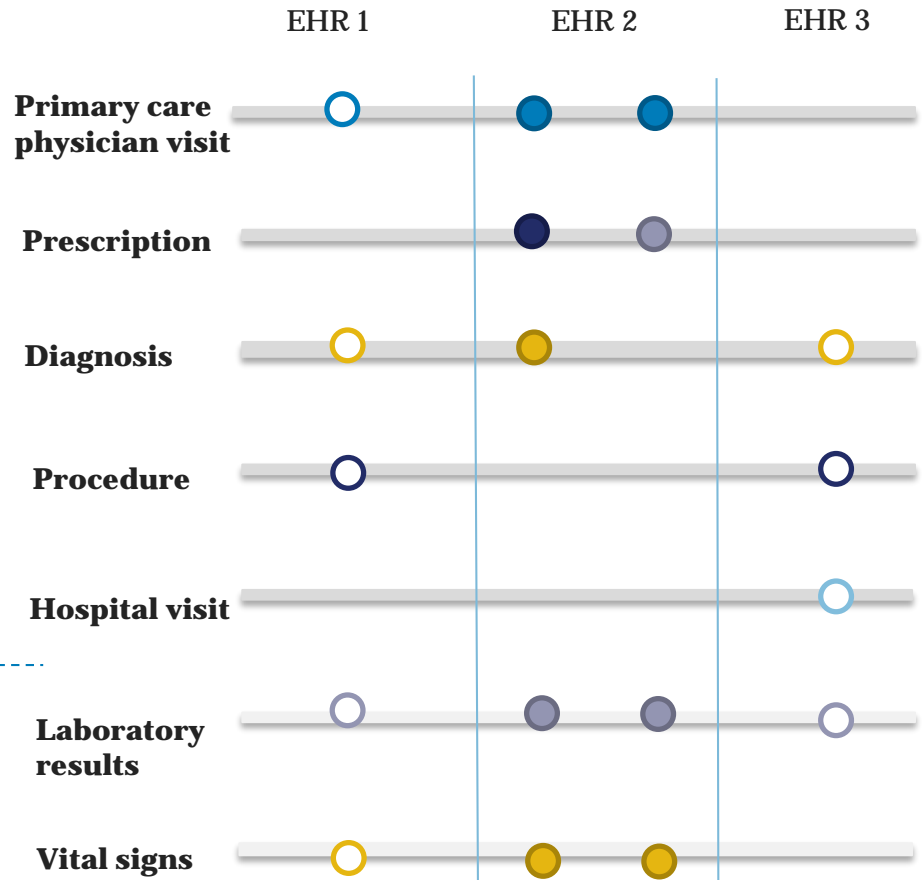
Comparing Claims Data vs. EHR Data

Claims Data

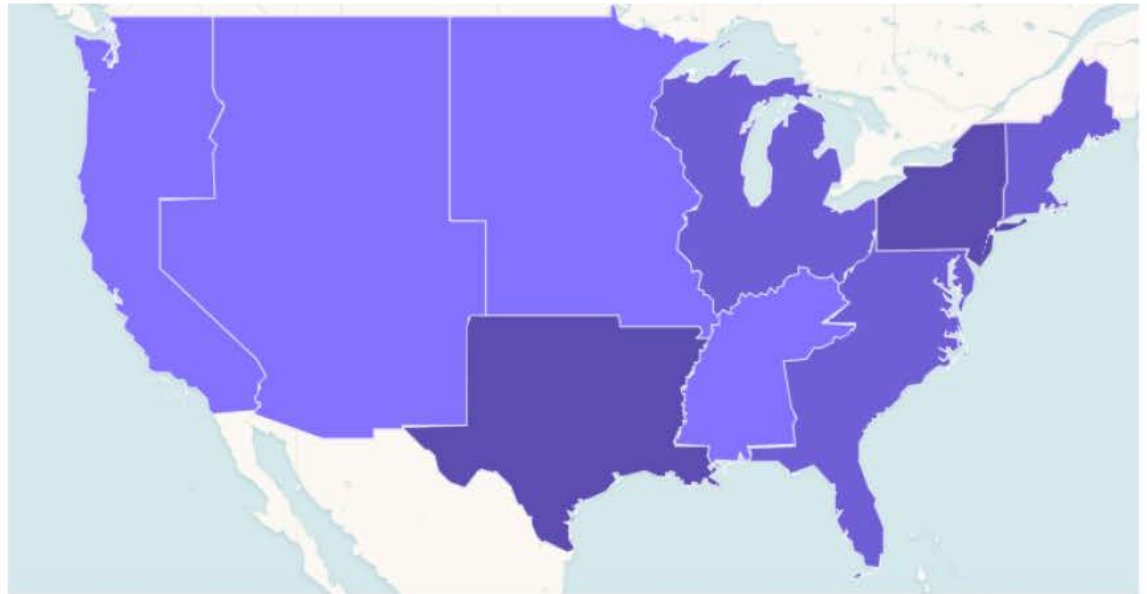Comprehensive data across all encounters and settings
Miss some clinical detail

Primary care physician visit			
Dispensing			
Diagnosis			
Procedure			
Hospital visit			
Laboratory results			
Vital signs			

EHR Data

Detailed data within a single encounter that miss other encounters

EHR 1   EHR 2   EHR 3

- **Primary care physician visit**
- **Prescription**
- **Diagnosis**
- **Procedure**
- **Hospital visit**
- **Laboratory results**
- **Vital signs**

Solid circles = captured data; Open circles = missing data

COVID-19 Geographic Distribution

US Regions	Patients	Percent
New England	1,700	13%
Middle Atlantic	3,280	26%
East North Central	1,400	11%
West North Central	620	5%
South Atlantic	1,690	13%
East South Central	320	3%
West South Central	2,850	23%
Mountain	610	5%
Pacific	130	1%

Patient location is determined by location of HCO headquarters

COVID-19 Codes

Antigen Lab Testing LOINC Codes

Code	Description
94307-6	SARS CoV 2 N gene [Presence] in Unspec specimen by NAA using primer-probe set N1
94308-4	SARS CoV 2 N gene [Presence] in Unspec specimen by NAA using primer-probe set N2
94309-2	SARS CoV 2 RNA [Presence] in Unspec specimen by NAA with probe detect
94310-0	SARS-like CoV N gene [Presence] in Unspec specimen by NAA with probe detect
94311-8	SARS CoV 2 N gene [Cycle Threshold #] in Unspec specimen by NAA using primer-probe set N1
94312-6	SARS CoV 2 N gene [Cycle Threshold #] in Unspec specimen by NAA using primer-probe set N2
94313-4	SARS-like CoV N gene [Cycle Threshold #] in Unspec specimen by NAA with probe detect
94314-2	SARS CoV 2 RdRp gene [Presence] in Unspec specimen by NAA with probe detect
94315-9	SARS CoV 2 E gene [Presence] in Unspec specimen by NAA with probe detect
94316-7	SARS CoV 2 N gene [Presence] in Unspec specimen by NAA with probe detect
94500-6	SARS CoV 2 RNA [Presence] in Resp specimen by NAA with probe detect
94502-2	SARS-related CoV RNA [Presence] in Resp specimen by NAA with probe detect
94509-7	SARS CoV 2 E gene [Cycle Threshold #] in Unspec specimen by NAA with probe detect
94510-5	SARS CoV 2 N gene [Cycle Threshold #] in Unspec specimen by NAA with probe detect
94511-3	SARS CoV 2 ORF1ab region [Cycle Threshold #] in Unspec specimen by NAA with probe detect
94533-7	SARS CoV 2 N gene [Presence] in Resp specimen by NAA with probe detect
94534-5	SARS CoV 2 RdRp gene [Presence] in Resp specimen by NAA with probe detect
94559-2	SARS CoV 2 ORF1ab region [Presence] in Resp specimen by NAA with probe detect
94565-9	SARS CoV 2 RNA [Presence] in Nasopharynx by NAA with non-probe detect
94639-2	SARS CoV 2 ORF1ab region [Presence] in Unspec specimen by NAA with probe detect
94640-0	SARS CoV 2 S gene [Presence] in Resp specimen by NAA with probe detect
94641-8	SARS CoV 2 S gene [Presence] in Unspec specimen by NAA with probe detect
94642-6	SARS CoV 2 S gene [Cycle Threshold #] in Resp specimen by NAA with probe detect
94643-4	SARS CoV 2 S gene [Cycle Threshold #] in Unspec specimen by NAA with probe detect
94644-2	SARS CoV 2 ORF1ab region [Cycle Threshold #] in Resp specimen by NAA with probe detect
94645-9	SARS CoV 2 RdRp gene [Cycle Threshold #] in Unspec specimen by NAA with probe detect
94646-7	SARS CoV 2 RdRp gene [Cycle Threshold #] in Resp specimen by NAA with probe detect
94647-5	SARS-related CoV RNA [Presence] in Unspec specimen by NAA with probe detect
94660-8	SARS CoV 2 RNA [Presence] in Serum or Plasma by NAA with probe detect

ICD-10 Diagnosis Codes

Code	Description
B97.29	Other CoV as the cause of diseases classified elsewhere
U07.1	COVID-19, virus identified
B34.2	CoV infection, Unspec site
J12.81	Pneumonia due to SARS-associated CoV
B97.2	CoV as the cause of diseases classified elsewhere
B97.21	SARS-associated CoV causing diseases classified elsewhere

Antibody Lab Testing LOINC Codes

Code	Description
94505-5	SARS-CoV-2 (COVID19) IgG Ab [Units/volume] in Serum or Plasma by Immunoassay
94506-3	SARS-CoV-2 (COVID19) IgM Ab [Units/volume] in Serum or Plasma by Immunoassay

Impact of rounding of the estimates to the nearest 10th

Numerator	Denominator	%		Numerator	Denominator	%
20	580	3.45		20	580	3.45
19	580	3.28		20	579	3.45
18	580	3.1		20	578	3.46
17	580	2.93		20	577	3.47
16	580	2.76		20	576	3.47
15	580	2.59		20	575	3.48
14	580	2.41		20	574	3.48
13	580	2.24		20	573	3.49
12	580	2.07		20	572	3.5
11	580	1.9		20	571	3.5