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Research Article

The Coviral Portal: Multi-Cohort Viral Loads and Antigen-Test Virtual Trials for COVID-19

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SUPPLEMENTARY METHODS

Institutional review

Institutional Review Board approval was obtained for all described work under Beth Israel Lahey Health (BILH) IRBs 2022P000328 and 2022P000288. The Harvard T. H. Chan School of Public Health IRB20-1979 provided non-human subjects research determination for virus culture work.

Defining specific patient groups

For the electronic records review arm of the study, we extracted information from the clinical-research data repository of Beth Israel Deaconess Medical Center Boston, a 743-bed tertiary-care teaching hospital, for each positive result for PCR tests for COVID-19 that had been performed in the course of routine clinical care between March 2020 and April 2023. Written consent was waived by the IRB because this was a records review study only, presenting minimal risk to patients. The following information was extracted: the patient's demographics (age, gender, and self-reported race/ethnicity), socioeconomic status (using the median neighborhood household income for the patient's ZIP code, obtained via the 2020 U.S. census, as a proxy), care setting (inpatient, outpatient, emergency ward, or other institution), presentation/disposition (based on vital signs, which we combined into a measure of initial presentation), outcome (survived, died with COVID-19 as the cause of death, died with COVID-19 as an incidental finding), vaccination status (vaccinated, unvaccinated, or unknown), treatment (CPT-encoded procedures, remdesivir (GS-5734; Gilead Sciences, Foster City, CA) administration, steroid administration), comorbidities (according to the Charlson Comorbidity Index (CCI): body-mass index, diabetes, chronic heart disease, chronic lung disease, chronic renal disease, liver disease, dementia, chronic neurological conditions, connective-tissue disease, Human Immunodeficiency Virus (HIV), and malignancy), and immunosuppression status (CD4+ T-count <100 cells/μL, hematologic malignancy, chemo/immuno-modulating agent alone or in setting of solid malignancy, organ transplant, or rheumatologic/inflammatory condition) [1,2]. The rationale for extracting these data items specifically was twofold: first, this list includes the complete COVID-19 core diagnostic data at federal and state levels; second, it includes data necessary for calculating the well validated 4C mortality score for SARS-CoV-2 [3]. ICD-10 codes corresponding to the listed comorbidities were determined by a physician (Dr. Arnaout) following prior methodologies but updated for 2022-2023. Gender of the patient was inferred from the database record created for each sample at its time of collection [4].

At presentation, patients were considered sick if any of the following were true within 1 day of the PCR test sample: systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, heart rate >100 beats per minute, respiratory rate >18 breaths per minute, or temperature >99.1 °F. They were otherwise considered well, with the exception that if no values were recorded (NULL in the data repository) for all criteria, presentation was considered unknown and therefore not assigned.

Patients were designated as immunocompromised at the time of PCR testing if one of the following were true: on their most recent T-cell subset analysis report, their absolute CD4+ cell count was <100 cells/μl; they had a diagnosis of either lymphoma or leukemia associated with a healthcare encounter (visit, admission, or phone call) either before the PCR test or within 60 days after the PCR test; they were on any of the following medications on an ongoing basis, prescribed prior to the PCR test and with enough refills to include the time up to 30 days prior to the PCR test: abatacept, adalimumab, anakinra, azathioprine, basiliximab, budesonide, certolizumab, cyclosporine, daclizumab, dexamethasone, everolimus, etanercept, golimumab, infliximab, ixekizumab, leflunomide, lenalidomide, methotrexate, mycophenolate, natalizumab, pomalidomide, prednisone, rituximab, secukinumab, serolimus, tacrolimus,

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tocilizumab, tofacitinib, ustekinumab, or vedolizumab. Otherwise, they were designated not immunocompromised.

Supplementary Table 1 provides further details for the above methods.

Viral load

The SARS-CoV-2 RT-qPCR testing in this study was performed on three Abbott molecular platforms: m2000, Alinity m, and Alinity 4-Plex (Abbott Molecular, Des Plaines, IL, USA). These detect identical SARS-CoV-2 N and RdRp gene targets. They are extremely sensitive, with LOD of ~100 copies/mL. They output a quantitative Fractional Cycle Number (FCN), a type of Ct value described in detail elsewhere [5]. Together these platforms accounted for 46,726 positive tests.

Ct values were converted to viral loads in units of copies of viral mRNA per mL using the public Python package ct2vl as previously reported [6]. Briefly, this software was validated via calibration curves established for all platforms using an extended SeraCare panel (LGC Seracare, Milford, MA) panel based on a SARS-CoV-2 genome incorporated into replication-incompetent, enveloped Sindbis virus and calibrated based on digital PCR at US National Institutes of Standards and Technology (NIST) and LGC/Seracare [7]. Validation material ranged in viral load from 300 to 106 viral genome copies/mL. Results were harmonized with the cycle threshold for a spiked internal control also amplified in each SARS-CoV-2 assay to confirm lack of PCR inhibition and accurate viral load output. The standards, modeling SARS-CoV-2 virus, were run through all stages of sample preparation and extraction to allow appropriate comparison with identically processed patient samples. R2 was ~0.99 for all calibration determinations, indicating assays are robustly quantitative.

Presumed SARS CoV-2 variant

Presumed variant was inferred from the date of sample collection based on the data presented by covariants showing the frequency of sequencing particular variants in Massachusetts, the United States, and other locations [8]. Specimens from before June 7, 2021 were annotated as being an early variant. Specimens from between July 7, 2021 and December 6, 2021 were annotated delta variant. Specimens from after January 3, 2022 were annotated as omicron variant. Results from the month between windows, when more than one major variant was common, were not annotated with a presumed variant and are omitted from by-variant comparisons.

Evaluation of antigen tests vs. PCR

Patients seeking COVID testing at a drive-through testing site near Boston affiliated with our medical center between May 23 and November 4 of 2022 were offered the opportunity to participate in a separate arm, providing a comparative, parallel prospective study [9,10]. Patients in this arm of the study provided verbal consent to participate; the IRB waived written consent due to a concern that contact with written materials would pose an undue risk of transmission of the virus, out-weighing the minimal risk of this study. Both symptomatic and asymptomatic individuals, with diverse demographics (age, race, sex, socio-economic status), were enrolled. Each patient who consented had both a standard-of-care PCR tests and two OTC antigen tests performed (Abbott BinaxNow COVID-19 Ag card and care start COVID-19 antigen home test). The PCR test was performed on material collected with a nasopharyngeal swab. SARS-CoV-2 RT-qPCR testing was performed using the Abbott m2000 real time or Alinity m SARS-CoV-2 assays according to the manufacturer's instructions, yielding, for each positive sample, a Ct value which was converted to viral load as previously described. Specimens for the antigen tests were collected with separate nasal swabs for each test, according to the manufacturer's instructions. These were collected and the tests performed by study personnel after informed consent was obtained on-site within the time-frame constraints detailed in each test's instructions for use, as per IRB. In order to extrapolate antigen-test performance from this subset to all patients, positivity vs. viral load was modeled by logistic regression (the logistic regression function in Python's scikit-learn library) [11]. Logistic Regression converges on optimal parameters in a model predicting the probability of a positive test based on viral load. Parameters were predicted separately for each test. The equation for probability was a standard sigmoid constrained to the range 0-1 (i.e., the lowest probability is zero and the highest probability is 1): p(test success) = $\frac{1}{1+e^{-k(v-v_0)}}$ where v, the independent variable, is log10 of the viral load. This constraint leaves two free parameters: v0 is the midpoint, i.e. the model's estimate of where the success rate passes 50%, while k controls the steepness, i.e. the change in viral load to change in probability of being positive.

Antigen tests and performance

In the head-to-head comparison of PCR and antigen test results, 281 patients consented to participate. Of the PCR samples collected, 277 were tested; the remaining four were mishandled or leaked. Of the 277, 65 had a positive COVID-19 result by PCR (23%). PCR-positive samples were tested on either the Alinity m SARS-CoV-2 real time RT-PCR assay or the Alinity m Resp-4-Plex PCR assay. Viral loads in the PCR-positive patients ranged from approximately 10 to approximately 109 copies/mL, with a peak in the distribution between 106 and 108. Of the 65 positive samples, three were sequenced and 20 selected at random were used to assess contagiousness in viral culture.

Of 65 patients with positive PCR tests, 43 tested positive on the Binax antigen test and 40 tested positive on the CareStart antigen test. No invalid antigen tests (lacking the control line) were observed. Only one of the patients who tested negative by PCR tested positive on the antigen tests (both Binax and CareStart), confirming the high specificity of these tests. The proportion of positive antigen tests varied with viral load. At viral loads less than 103 copies/mL, both antigen tests were always negative; at viral loads greater than 107 copies/mL, both were always positive. However, there was an overlap of antigen-test-positive and antigen-test-negative results at intermediate viral loads (Figure 3a). k and v0 values (see Methods) were comparable between the two tests (k=1.184, v0=4.538 for Binax and k=1.142, v0=4.995 for CareStart). The resulting S-shaped curves were used to predict antigen test performance in the web portal.

Contagiousness

As freeze-thaw does not impact viral viability, samples from the comparative study were stored at 4°C until contagiousness testing, which was done within a four-day time period on a random sample of the PCR-positive samples. Quantitative viral culture was performed using Vero E6 cells (ATCC CRL-1586) seeded on a 6-well flat bottom plate at 0.3×106 cells per well in Eagle's Minimum

Essential Media (EMEM) containing 1% antibiotic-antimycotic, 1% HEPES and 5% fetal calf serum (FCS, Gibco), grown to confluence at approximately 1 × 106 cells per well, inoculated with 250 µL of patient sample, and incubated at 37˚C for 24 hours for viral adsorption, as previously described [12-15]. Carryover of non-viable viral RNA present in samples was limited by washing cell cultures after the 24-hour viral adsorption and adding fresh EMEM composite media with reduced FCS to 2% for viral growth, meaning detectable virus represents viable replicating virus. On days 3 and 6, cell culture supernatant was removed and added to 800 µL of VXL buffer (QIAGEN, German, MD) (1:1 ratio) for subsequent nucleic acid extraction and detection of virus by PCR. Viral load in culture supernatants on days 3 and 6 served as a quantitative surrogate for viable (i.e. replication-competent) virus in the patient sample and provided a measure of the magnitude of sample infectivity. SARS-CoV-2 RT-qPCR testing of vero cell culture supernatants was performed using the Abbott m2000 Real-Time or Alinity m SARS-CoV-2 assays according to the manufacturer's instructions. The contagiousness threshold was determined by the threshold patient-sample viral load value resulting in detectable culture viral load.

Whole-genome viral NGS

Next-Generation-Sequencing (NGS)-based sequencing of select PCR-positive samples from the viral antigen evaluation study was performed as follows. Full-length SARS-CoV-2 viral genome sequencing was performed on the Oxford Nanopore MinION system (≥R9.4 flowcell; Oxford Nanopore Technologies-ONT, Oxford, UK) using the guppy base caller and the downstream ARTIC network bioinformatics pipeline for genome assembly [16,17]. The workflow was run on a 2021 Intel Core i9-11900 Rocket Lake 3.5 GHz 8-cores LGA 1200 boxed processor with NVIDIA A5000 GPU. Standard coverage and quality metrics and plots were produced, single-nucleotide variants were recorded, and variants assigned using NextClade [18].

Web portal and privacy protection

The portal was written using Svelte and d3 for the interactive frontend and Python run against a Postgres database for the backend. To reduce re-identification risk, ages were jittered by adjusting the patient's date of birth by a random number of days (drawn from a Gaussian distribution with a standard deviation of two years) before calculating patient's age at the time of each test. Groups smaller than 4-8 patients are suppressed and therefore not viewable. Revealing exact sizes of such small groups defined by multiple patient characteristics would pose a re-identification risk. To prevent inferring the sizes of these groups by subtraction of viewable group sizes, viewable group sizes are jittered by dropping approximately 0.5%-1% of the data on any split by patient feature. To maximize consistency of the results of jittering as data are updated, jittering was performed using random number seeds based on pseudo-identifiers (which are never uploaded and thus inaccessible to/safe from the web client). For ease of visualization, plots of viral load distributions are shown as kernel-density estimates (i.e. smoothed) using a Gaussian kernel of width 0.25 log10 viral load units (~1.7-fold).

Statistical tests

The geometric mean viral load for each patient group was calculated as a summary statistic. The geometric (as opposed to arithmetic) mean was chosen because viral loads vary over many orders of magnitude [19]. The Kolmogorov-Smirnov test (KS; scipy.stats.kstest) was used to compare distributions. This test was used because data were not distributed normally and KS does not require normality (unlike, for example, the t-test, which requires normal distributions). KS tests the null hypothesis that the distributions of viral loads for two patient groups are statistically indistinguishable [20]. The p-value gives the probability that distributions from the two groups are drawn from the same underlying distribution. A large p-value means the two groups are statistically indistinguishable; a small p-value means they are different. Interpretation of p-values as significant vs. not significant requires a significance threshold, which requires correction for multiple comparisons if multiple comparisons are performed [21,22]. Because the number of comparisons performed via the web portal is up to the user, uncorrected p-values are reported, with interpretation as significant or not significant left to the user.

Software and hardware

Data extraction, annotation, statistics, and analyses were performed using standard Unix tools and Python 3.9+ using the pandas, numpy, scipy, and scikit libraries and the interactive Jupyter notebook environment. Figures were created using Python graphics libraries matplotlib and seaborn, and OmniGraffle 7 (The Omni Group, Seattle, WA), or by custom JavaScript/d3/Svelte components on the web portal.

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SUPPLEMENTARY TABLE AND FIGURES

Table S1: Definitions for clinical annotations: Listed are ICD-10 codes and other methods for determination of clinical annotations.

Checkbox name	Notes
Acquired immunodeficiency syndrome	ICD10 codes: ["B20","O98711","O98712","O98713","O98719","O9872","O9873","Z21"]
Age	years
Blood products	CPT4 codes: ["P9012","P9016","P9047","P9059","P9073"]
BMI	kilograms/(meter**2); allowed values: {"Underweight": "bmi < 18.5 AND age > 17", "Healthy weight": "bmi >= 18.5 AND bmi < 25 AND age > 17", "Overweight": "bmi >= 25 AND bmi < 30 AND age > 17", "Obese": "bmi >= 30 AND age > 17"}
Cancer	ICD10 codes: ['C000', 'C001', 'C002', 'C003', 'C004', 'C005', 'C006', 'C008', 'C009', 'C01', 'C020', 'C021', 'C022', 'C023', 'C024', 'C028', 'C029', 'C030', 'C031', 'C039', 'C040', 'C041', 'C048', 'C049', 'C050', 'C051', 'C052', 'C058', 'C059', 'C060', 'C061', 'C062', 'C0680', 'C0689', 'C069', 'C07', 'C080', 'C081', 'C089', 'C090', 'C091', 'C098', 'C099', 'C100', 'C101', 'C102', 'C103', 'C104', 'C108', 'C109', 'C110', 'C111', 'C112', 'C113', 'C118', 'C119', 'C12', 'C130', 'C131', 'C132', 'C138', 'C139', 'C140', 'C142', 'C148', 'C153', 'C154', 'C155', 'C158', 'C159', 'C160', 'C161', 'C162', 'C163', 'C164', 'C165', 'C166', 'C168', 'C169', 'C170', 'C171', 'C172', 'C173', 'C178', 'C179', 'C180', 'C181', 'C182', 'C183', 'C184', 'C185', 'C186', 'C187', 'C188', 'C189', 'C19', 'C20', 'C210', 'C211', 'C212', 'C218', 'C220', 'C221', 'C222', 'C223', 'C224', 'C227', 'C228', 'C229', 'C23', 'C240', 'C241', 'C248', 'C249', 'C250', 'C251', 'C252', 'C253', 'C254', 'C257', 'C258', 'C259', 'C260', 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Connective tissue disease	ICD10 codes: ['M05', 'M06', 'M315', 'M32', 'M33', 'M34', 'M351', 'M353', 'M360']
Presentation	Sick-appearing (any of systolic blood pressure <90 mmHg, diastoloc blood pressure <60 mmHg, heart rate >100 beats per minute, respiratory rate >18 breaths per minute, or temperature >99.1°F within 1 day of PCR test sample) vs. well-appearing
Vaccination status	Vaccinated vs. unvaccinated vs. unknown
Dexamethasone	matches to case-insensitive searches for the string "dexamethasone"
Diabetes	ICD10 codes:['E0800', 'E0801', 'E0810', 'E0811', 'E0821', 'E0822', 'E0829', 'E08311', 'E08319', 'E08321', 'E083211', 'E083212', 'E083213', 'E083219', 'E08329', 'E083291', 'E083292', 'E083293', 'E083299', 'E08331', 'E083311', 'E083312', 'E083313', 'E083319', 'E08339', 'E083391', 'E083392', 'E083393', 'E083399', 'E08341', 'E083411', 'E083412', 'E083413', 'E083419', 'E08349', 'E083491', 'E083492', 'E083493', 'E083499', 'E08351', 'E083511', 'E083512', 'E083513', 'E083519', 'E083521', 'E083522', 'E083523', 'E083529', 'E083531', 'E083532', 'E083533', 'E083539', 'E083541', 'E083542', 'E083543', 'E083549', 'E083551', 'E083552', 'E083553', 'E083559', 'E08359', 'E083591', 'E083592', 'E083593', 'E083599', 'E0836', 'E0837X1', 'E0837X2', 'E0837X3', 'E0837X9', 'E0839', 'E0840', 'E0841', 'E0842', 'E0843', 'E0844', 'E0849', 'E0851', 'E0852', 'E0859', 'E08610', 'E08618', 'E08620', 'E08621', 'E08622', 'E08628', 'E08630', 'E08638', 'E08641', 'E08649', 'E0865', 'E0869', 'E088', 'E089', 'E0900', 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Checkbox name	Notes
Disabilities	ICD10 codes: ['G041', 'G800', 'G801', 'G802', 'G808', 'G809', 'G8100', 'G8101', 'G8102', 'G8103', 'G8104', 'G8110', 'G8111', 'G8112', 'G8113', 'G8114', 'G8190', 'G8191', 'G8192', 'G8193', 'G8194', 'G8220', 'G8221', 'G8222', 'G8250', 'G8251', 'G8252', 'G8253', 'G8254', 'G830', 'G8310', 'G8311', 'G8312', 'G8313', 'G8314', 'G8320', 'G8321', 'G8322', 'G8323', 'G8324', 'G8330', 'G8331', 'G8332', 'G8333', 'G8334', 'G834', 'G835', 'G8381', 'G8382', 'G8383', 'G8384', 'G8389', 'G839', '169031', '169032', '169033', '169034', '169039', '169041', '169042', '169043', '169044', '169049', '169051', '169052', '169053', '169054', '169059', '169061', '169062', '169063', '169064', '169065', '169069', '169131', '169132', '169133', '169134', '169139', '169141', '169142', '169143', '169144', '169149', '169151', '169152', '169153', '169154', '169159', '169161', '169162', '169163', '169164', '169165', '169169', '169231', '169232', '169233', '169234', '169239', '169241', '169242', '169243', '169244', '169249', '169251', '169252', '169253', '169254', '169259', '169261', '169262', '169263', '169264', '169265', '169269', '169331', '169332', '169333', '169334', '169339', '169341', '169342', '169343', '169344', '169349', '169351', '169352', '169353', '169354', '169359', '169361', '169362', '169363', '169364', '169365', '169369', '169831', '169832', '169833', '169834', '169839', '169841', '169842', '169843', '169844', '169849', '169851', '169852', '169853', '169854', '169859', '169861', '169862', '169863', '169864', '169865', '169869', '169931', '169932', '169933', '169934', '169939', '169941', '169942', '169943', '169944', '169949', '169951', '169952', '169953', '169954', '169959', '169961', '169962', '169963', '169964', '169965', '169969', 'Q', 'R532']
Heart conditions	ICD10 codes:['A1884', 'A3282', 'A3681', 'A381', 'A395', 'A5203', 'B2682', 'B332', 'B376', 'B5881', 'C452', 'D8685', 'G130', 'G712', 'G713', 'G720', 'G721', 'G722', 'G7249', 'G7281', 'G7289', 'G729', 'G737', 'I01', 'I02', 'I05', 'I06', 'I07', 'I08', 'I09', 'I0981', 'I11', 'I110', 'I13', 'I130', 'I20', 'I21', 'I22', 'I23', 'I24', 'I25', 'I252', 'I3', 'I4', 'I5', 'I501', 'I5020', 'I5021', 'I5022', 'I5023', 'I5030', 'I5031', 'I5032', 'I5033', 'I5040', 'I5041', 'I5042', 'I5043', 'I50810', 'I50811', 'I50812', 'I50813', 'I50814', 'I5082', 'I5083', 'I5084', 'I5089', 'I509', 'I5181', 'I70', '19713', '197130', '197131', 'J1082', 'J1182', 'O101', 'O29121', 'O29122', 'O29123', 'O29129', 'O903', 'OO2912', 'Q2', 'R570', 'S26', 'T82', 'Z95', 'Z95811', 'Z95812']
Immune status	Immunosuppressed vs. immunocompetent. Immunosuppresed if most recent T-cell subset analysis report, their absolute CD4 cell count was <100 cells/µl; they had a diagnosis of either lymphoma or leukemia associated with an encounter either before the PCR test or within 60 days of the PCR test; they were on any of the following drugs on an ongoing basis, prescribed prior to the PCR test and with enough refills to include the time up to 30 days prior to the PCR test: abatacept, adalimumab, anakinra, azathioprine, basiliximab, budesonide, certolizumab, cyclosporine, daclizumab, dexamethasone, everolimus, etanercept, golimumab, infliximab, ixekizumab, leflunomide, lenalidomide, methotrexate, mycophenolate, natalizumab, pomalidomide, prednisone, rituximab, secukinumab, serolimus, tacrolimus, tocilizumab, tofacitinib, ustekinumab, or vedolizumab. Otherwise, immunocompetent
Liver disease	ICD10 codes: ['A5145', 'A5274', 'B180', 'B181', 'B182', 'B188', 'B189', 'B190', 'B1910', 'B1911', 'B1920', 'B1921', 'B199', 'B251', 'B581', 'I8500', 'I8501', 'I8510', 'I8511', 'I864', 'K700', 'K702', 'K7030', 'K7031', 'K7040', 'K7041', 'K709', 'K713', 'K714', 'K7150', 'K7151', 'K716', 'K717', 'K718', 'K7210', 'K7211', 'K7290', 'K7291', 'K730', 'K731', 'K732', 'K738', 'K739', 'K740', 'K7400', 'K7401', 'K7402', 'K741', 'K742', 'K743', 'K744', 'K745', 'K7460', 'K7469', 'K751', 'K752', 'K753', 'K754', 'K7581', 'K7589', 'K759', 'K760', 'K761', 'K762', 'K763', 'K764', 'K765', 'K766', 'K767', 'K7681', 'K7689', 'K769', 'K77', 'K9182', 'Z944']
Mental health conditions	ICD10 codes:['F060', 'F061', 'F062', 'F0630', 'F0631', 'F0632', 'F0633', 'F0634', 'F11150', 'F11151', 'F11159', 'F11250', 'F11251', 'F11259', 'F11950', 'F11951', 'F11959', 'F12150', 'F12151', 'F12159', 'F12250', 'F12251', 'F12259', 'F12950', 'F12951', 'F12959', 'F13150', 'F13151', 'F13159', 'F13250', 'F13251', 'F13259', 'F13950', 'F13951', 'F13959', 'F14150', 'F14151', 'F14159', 'F14250', 'F14251', 'F14259', 'F14950', 'F14951', 'F14959', 'F15150', 'F15151', 'F15159', 'F15250', 'F15251', 'F15259', 'F15950', 'F15951', 'F15959', 'F16150', 'F16151', 'F16159', 'F16250', 'F16251', 'F16259', 'F16950', 'F16951', 'F16959', 'F18150', 'F18151', 'F18159', 'F18250', 'F18251', 'F18259', 'F18950', 'F18951', 'F18959', 'F19150', 'F19151', 'F19159', 'F19250', 'F19251', 'F19259', 'F19950', 'F19951', 'F19959', 'F200', 'F201', 'F202', 'F203', 'F205', 'F2081', 'F2089', 'F209', 'F21', 'F22', 'F23', 'F24', 'F250', 'F251', 'F258', 'F259', 'F28', 'F29', 'F3010', 'F3011', 'F3012', 'F3013', 'F302', 'F303', 'F304', 'F308', 'F309', 'F310', 'F3110', 'F3111', 'F3112', 'F3113', 'F312', 'F3130', 'F3131', 'F3132', 'F314', 'F315', 'F3160', 'F3161', 'F3162', 'F3163', 'F3164', 'F3170', 'F3171', 'F3172', 'F3173', 'F3174', 'F3175', 'F3176', 'F3177', 'F3178', 'F3181', 'F3189', 'F319', 'F320', 'F321', 'F322', 'F323', 'F324', 'F325', 'F328', 'F3281', 'F3289', 'F329', 'F32A', 'F330', 'F331', 'F332', 'F333', 'F3340', 'F3341', 'F3342', 'F338', 'F339', 'F340', 'F341', 'F348', 'F3481', 'F3489', 'F349', 'F39', 'F4489', 'F843']
Neighborhood income	median household income by zip code from the 2020 Census (2020 American Community Survey). URL structure (replace <ZIPCODE> with an actual zipcode): https://api.census.gov/data/2020/acs/acs5/subject?get=NAME,S1901_C01_012E&for=zip%20code%20tabulation%20area:<ZIPCODE> . In the text that this URL will return, S1901_C01_012E is the column name for median household income
Neurological disorders	ICD10 codes:['E7500', 'E7501', 'E7502', 'E7509', 'E7510', 'E7511', 'E7519', 'E7523', 'E7525', 'E7526', 'E7529', 'E754', 'F0150', 'F0151', 'F0280', 'F0281', 'F0390', 'F0391', 'F05', 'F842', 'G08', 'G10', 'G110', 'G111', 'G1110', 'G1111', 'G1119', 'G112', 'G113', 'G114', 'G118', 'G119', 'G120', 'G121', 'G1220', 'G1221', 'G1222', 'G1223', 'G1224', 'G1225', 'G1229', 'G128', 'G129', 'G131', 'G132', 'G138', 'G20', 'G210', 'G2111', 'G2119', 'G212', 'G213', 'G214', 'G218', 'G219', 'G230', 'G231', 'G232', 'G238', 'G239', 'G2409', 'G241', 'G242', 'G248', 'G254', 'G255', 'G2570', 'G2571', 'G2579', 'G2581', 'G2582', 'G2583', 'G2589', 'G259', 'G26', 'G300', 'G301', 'G308', 'G309', 'G3101', 'G3109', 'G311', 'G312', 'G3181', 'G3182', 'G3183', 'G3185', 'G3189', 'G319', 'G320', 'G3281', 'G3289', 'G35', 'G360', 'G368', 'G369', 'G370', 'G371', 'G372', 'G373', 'G374', 'G375', 'G378', 'G379', 'G40001', 'G40009', 'G40011', 'G40019', 'G40101', 'G40109', 'G40111', 'G40119', 'G40201', 'G40209', 'G40211', 'G40219', 'G40301', 'G40309', 'G40311', 'G40319', 'G40401', 'G40409', 'G40411', 'G40419', 'G4042', 'G40501', 'G40509', 'G40801', 'G40802', 'G40803', 'G40804', 'G40811', 'G40812', 'G40813', 'G40814', 'G40821', 'G40822', 'G40823', 'G40824', 'G40833', 'G40834', 'G4089', 'G40901', 'G40909', 'G40911', 'G40919', 'G40A01', 'G40A09', 'G40A11', 'G40A19', 'G40801', 'G40809', 'G40B11', 'G40819', 'G47411', 'G47419', 'G47421', 'G47429', 'G803', 'G890', 'G910', 'G911', 'G912', 'G913', 'G914', 'G918', 'G919', 'G930', 'G9340', 'G9341', 'G9349', 'G935', 'G936', 'G937', 'G9381', 'G9382', 'G9389', 'G939', 'G94', 'O99350', 'O99351', 'O99352', 'O99353', 'O99354', 'O99355', 'P9160', 'P9161', 'P9162', 'P9163', 'R561', 'R569']
Outcome	Died from COVID-19 (causal), Died with COVID-19 (incidental), Survived
Patient location	Inpatient, Outpatient, Emergency Room, or Institutional (sent from another hospital)
Peptic ulcer disease	ICD10 codes: ['K250', 'K251', 'K252', 'K253', 'K254', 'K255', 'K256', 'K257', 'K259', 'K260', 'K261', 'K262', 'K263', 'K264', 'K265', 'K266', 'K267', 'K269', 'K270', 'K271', 'K272', 'K273', 'K274', 'K275', 'K276', 'K277', 'K279', 'K280', 'K281', 'K282', 'K283', 'K284', 'K285', 'K286', 'K287', 'K289']
Peripheral vascular disease	ICD10 codes: ['A5200', 'A5201', 'A5202', 'A5209', '1700', '1701', '170201', '170202', '170203', '170208', '170209', '170211', '170212', '170213', '170218', '170219', '170221', '170222', '170223', '170228', '170229', '170231', '170232', '170233', '170234', '170235', '170238', '170239', '170241', '170242', '170243', '170244', '170245', '170248', '170249', '17025', '170261', '170262', '170263', '170268', '170269', '170291', '170292', '170293', '170298', '170299', '170301', '170302', '170303', '170308', '170309', '170311', '170312', '170313', '170318', '170319', '170321', '170322', '170323', '170328', '170329', '170331', '170332', '170333', '170334', '170335', '170338', '170339', '170341', '170342', '170343', '170344', '170345', '170348', '170349', '17035', '170361', '170362', '170363', '170368', '170369', '170391', '170392', '170393', '170398', '170399', '170401', '170402', '170403', '170408', '170409', '170411', '170412', '170413', '170418', '170419', '170421', '170422', '170423', '170428', '170429', '170431', '170432', '170433', '170434', '170435', '170438', '170439', '170441', '170442', '170443', '170444', '170445', '170448', '170449', '17045', '170461', '170462', '170463', '170468', '170469', '170491', '170492', '170493', '170498', '170499', '170501', '170502', '170503', '170508', '170509', '170511', '170512', '170513', '170518', '170519', '170521', '170522', '170523', '170528', '170529', '170531', '170532', '170533', '170534', '170535', '170538', '170539', '170541', '170542', '170543', '170544', '170545', '170548', '170549', '17055', '170561', '170562', '170563', '170568', '170569', '170591', '170592', '170593', '170598', '170599', '170601', '170602', '170603', '170608', '170609', '170611', '170612', '170613', '170618', '170619', '170621', '170622', '170623', '170628', '170629', '170631', '170632', '170633', '170634', '170635', '170638', '170639', '170641', '170642', '170643', '170644', '170645', '170648', '170649', '17065', '170661', '170662', '170663', '170668', '170669', '170691', '170692', '170693', '170698', '170699', '170701', '170702', '170703', '170708', '170709', '170711', '170712', '170713', '170718', '170719', '170721', '170722', '170723', '170728', '170729', '170731', '170732', '170733', '170734', '170735', '170738', '170739', '170741', '170742', '170743', '170744', '170745', '170748', '170749', '17075', '170761', '170762', '170763', '170768', '170769', '170791', '170792', '170793', '170798', '170799', '1708', '17090', '17091', '17092', '17100', '17101', '17102', '17103', '1711', '1712', '1713', '1714', '1715', '1716', '1718', '1719', '1720', '1721', '1722', '1723', '1724', '1725', '1726', '1728', '1729', '17301', '1731', '17381', '17389', '1739', '17401', '17409', '17410', '17411', '17419', '1742', '1743', '1744', '1745', '1748', '1749', '175011', '175012', '175013', '175019', '175021', '175022', '175023', '175029', '17581', '17589', '1770', '1771', '1772', '1773', '1774', '1775', '1776', '17770', '17771', '17772', '17773', '17774', '17775', '17776', '17777', '17779', '177810', '177811', '177812', '177819', '17789', '1779', '1780', '1781', '1788', '1789', '1790', '1791', '1798', 'K551', 'Z95820', 'Z95828']
Pregnancy status	Pregnant or Recently delivered, Not pregnant. (males, individuals under 13 or over 56, and recent test results excluded from results)
Presumed variant	Early variants, delta, omicron
Pulmonary disease	ICD10 codes: ['J410', 'J411', 'J418', 'J42', 'J430', 'J431', 'J432', 'J438', 'J439', 'J440', 'J441', 'J449', 'J470', 'J471', 'J479', 'J60', 'J61', 'J620', 'J628', 'J630', 'J631', 'J632', 'J633', 'J634', 'J635', 'J636', 'J64', 'J65', 'J660', 'J661', 'J662', 'J668', 'J670', 'J671', 'J672', 'J673', 'J674', 'J675', 'J676', 'J677', 'J678', 'J679', 'J684', 'J701', 'J703']
Race/Ethnicity	self-reported. Allowed values: Black, White, Hispanic, Asian + Pacific Islander, Other + Unknown.
Remdesivir	matches to fuzzy-match case-insensitive searching for strings beginning "remd"
Renal disease	ICD10 codes: ['I120', 'I1311', 'I132', 'N183', 'N1830', 'N1831', 'N1832', 'N184', 'N185', 'N186', 'N189', 'N19', 'Z4901', 'Z4902', 'Z4931', 'Z4932', 'Z9115', 'Z940', 'Z992']
Sex	Female vs. male
Sickle cell & thalassemia	ICD10 codes: ["D56","D57"]
Smoking status	Current, former, never
Substance abuse	ICD10 codes: ['F1010', 'F1011', 'F10120', 'F10121', 'F10129', 'F10130', 'F10131', 'F10132', 'F10139', 'F1014', 'F10150', 'F10151', 'F10159', 'F10180', 'F10181', 'F10182', 'F10188', 'F1019', 'F1020', 'F1021', 'F10220', 'F10221', 'F10229', 'F10230', 'F10231', 'F10232', 'F10239', 'F1024', 'F10250', 'F10251', 'F10259', 'F1026', 'F1027', 'F10280', 'F10281', 'F10282', 'F10288', 'F1029', 'F1094', 'F10950', 'F10951', 'F10959', 'F1096', 'F1097', 'F10980', 'F11', 'F1110', 'F1111', 'F11120', 'F11121', 'F11122', 'F11129', 'F1113', 'F1114', 'F11181', 'F11182', 'F11188', 'F1119', 'F1120', 'F1121', 'F11220', 'F11221', 'F11222', 'F11229', 'F1123', 'F1124', 'F11281', 'F11282', 'F11288', 'F1129', 'F12', 'F1210', 'F1211', 'F12120', 'F12121', 'F12122', 'F12129', 'F1213', 'F12180', 'F12188', 'F1219', 'F1220', 'F1221', 'F12220', 'F12221', 'F12222', 'F12229', 'F1223', 'F12280', 'F12288', 'F1229', 'F1310', 'F1311', 'F13120', 'F13121', 'F13129', 'F13130', 'F13131', 'F13132', 'F13139', 'F1314', 'F13180', 'F13181', 'F13182', 'F13188', 'F1319', 'F1320', 'F1321', 'F13220', 'F13221', 'F13229', 'F13230', 'F13231', 'F13232', 'F13239', 'F1324', 'F1326', 'F1327', 'F13280', 'F13281', 'F13282', 'F13288', 'F1329', 'F14', 'F1410', 'F1411', 'F14120', 'F14121', 'F14122', 'F14129', 'F1413', 'F1414', 'F14180', 'F14181', 'F14182', 'F14188', 'F1419', 'F1420', 'F1421', 'F14220', 'F14221', 'F14222', 'F14229', 'F1423', 'F1424', 'F14280', 'F14281', 'F14282', 'F14288', 'F1429', 'F1510', 'F1511', 'F15120', 'F15121', 'F15122', 'F15129', 'F1513', 'F1514', 'F15180', 'F15181', 'F15182', 'F15188', 'F1519', 'F1520', 'F1521', 'F15220', 'F15221', 'F15222', 'F15229', 'F1523', 'F1524', 'F15280', 'F15281', 'F15282', 'F15288', 'F1529', 'F16', 'F1610', 'F1611', 'F16120', 'F16121', 'F16122', 'F16129', 'F1614', 'F16180', 'F16183', 'F16188', 'F1619', 'F1620', 'F1621', 'F16220', 'F16221', 'F16229', 'F1624', 'F16280', 'F16283', 'F16288', 'F1629', 'F1810', 'F1811', 'F18120', 'F18121', 'F18129', 'F1814', 'F1817', 'F18180', 'F18188', 'F1819', 'F1820', 'F1821', 'F18220', 'F18221', 'F18229', 'F1824', 'F1827', 'F18280', 'F18288', 'F1829', 'F19', 'F1910', 'F1911', 'F19120', 'F19121', 'F19122', 'F19129', 'F19130', 'F19131', 'F19132', 'F19139', 'F1914', 'F1916', 'F1917', 'F19180', 'F19181', 'F19182', 'F19188', 'F1919', 'F1920', 'F1921', 'F19220', 'F19221', 'F19222', 'F19229', 'F19230', 'F19231', 'F19232', 'F19239', 'F1924', 'F1926', 'F1927', 'F19280', 'F19281', 'F19282', 'F19288', 'F1929', 'G621', 'I426', 'K2920', 'K2921', 'K7010', 'K7011', 'O99310', 'O99311', 'O99312', 'O99313', 'O99314', 'O99315', 'O99320', 'O99321', 'O99322', 'O99323', 'O99324', 'O99325']
Tocilizumab	matches to case-insensitive searches for the string "tocilizumab"
Transplanted organ and tissue status	ICD10 codes: ["Z94"]
Ventilation assistance	CPT4 codes: ["94002", "94003", "94640", "94645"]

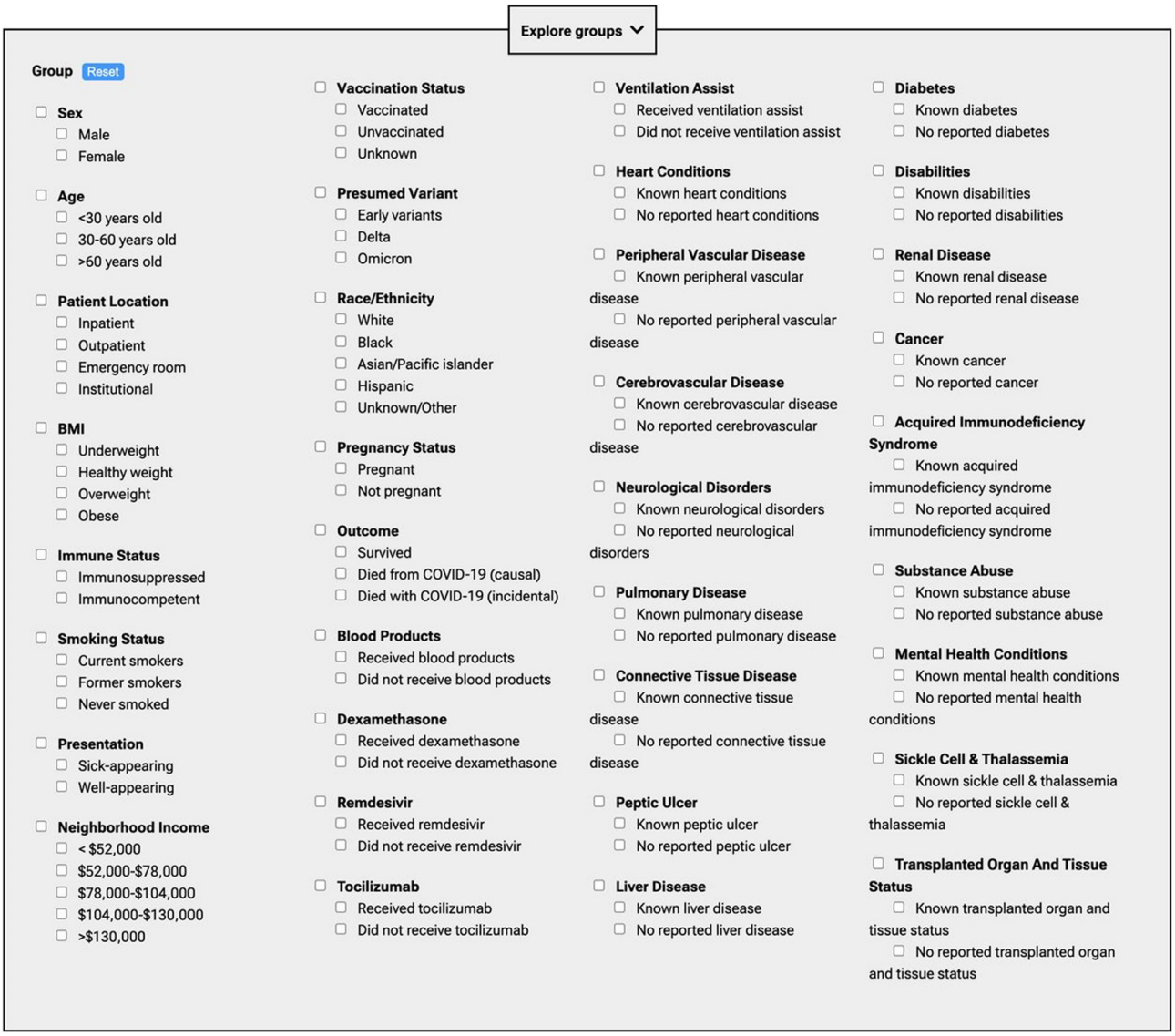

Figure S1: User-interface checkboxes: The web portal allows users to select cohorts by patient demographics, comorbidities, presentation, treatment, and socioeconomic status. Users can define and compare complex subgroups by selecting multiple characteristics via checkboxes, as shown.

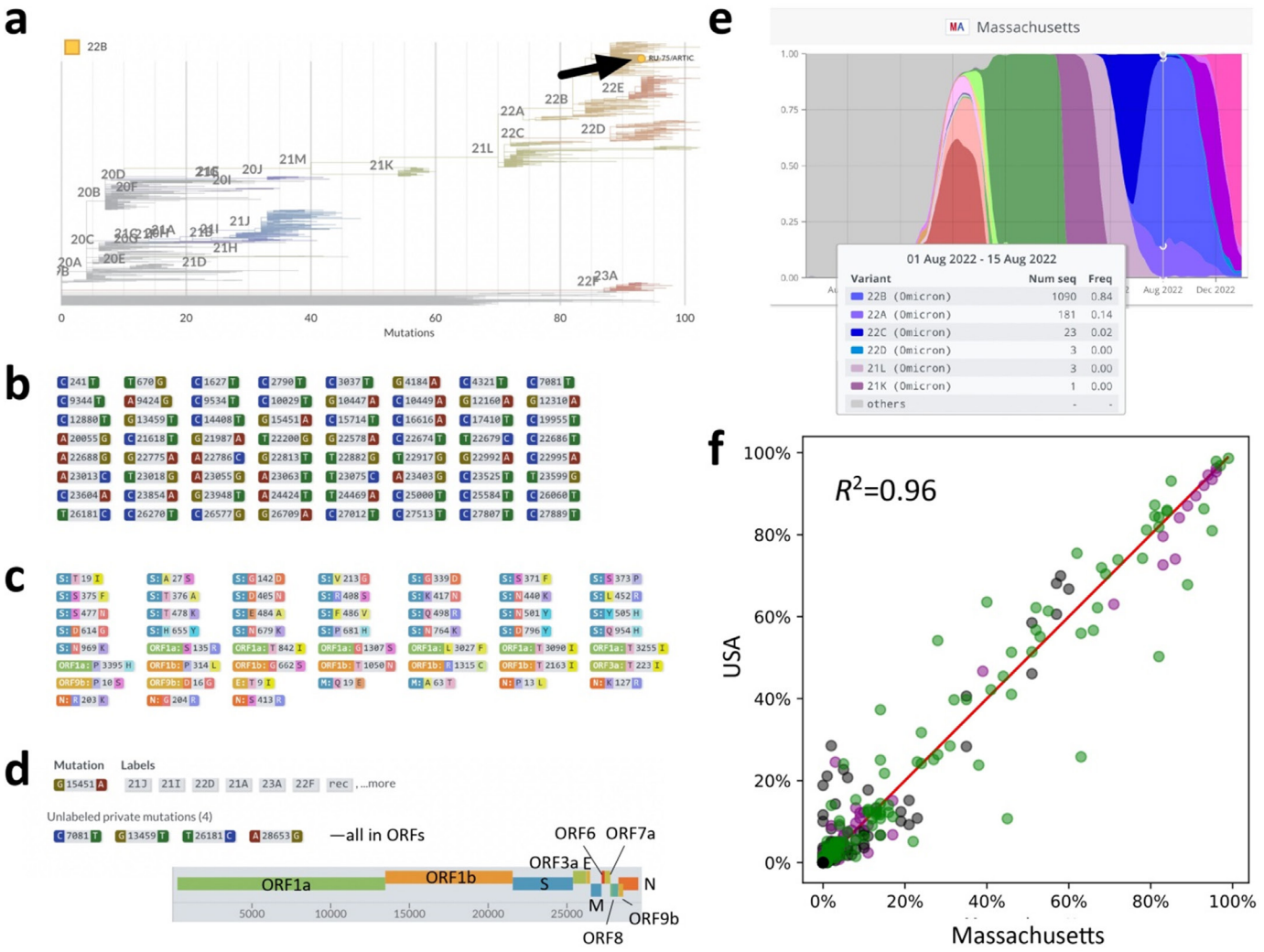

Figure S2: Sequencing late-2022 strain and generalizability of Massachusetts-level results to the United States as a whole. Results of sequencing of a BA5.2/Clade 22B patient sample from Aug 2022-Sep 2022 (97.6% coverage). (a) Sample relative to COVID-19 phylogeny (with clade labels). (b) First 64 of the 72 nucleotide substitutions relative to the original Wuhan strain. (c) 52 amino acid substitutions relative to the Wuhan strain. (d) The five unique ("private") mutations relative to the phylogenetic tree. (e) Distribution of strains in Massachusetts near the time of the sample according to covariants.org. (f) Comparison by frequency of the strains circulating in Massachusetts to those circulating in the United States at the same times demonstrating generalizability of Massachusetts-state variant patterns to the country as a whole. Red line, 1:1. Gray, early strains; purple, delta strains; green, omicron strains. R2 is for least-squares linear regression of USA vs. Massachusetts data (regression slope=0.97, intercept=0.00).