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Following the Science: the role of the academic medical center in the COVID-19 pandemic

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Following the Science: The Role of the Academic Medical Center in the COVID-19 Pandemic

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Introduction

Throughout the course of the COVOD-19 pandemic, leaders have frequently argued to effectively battle the impact of the SARS-CoV-2 virus on public health, everyone should "follow the science." However, in the early Spring of 2020 there was very little knowledge about exactly what was the science surrounding this virus. Further, very few tools had been developed to help guide the public. The nationwide testing capacity specific to SARS-CoV-2 was grossly inadequate. There were no established methods for biosurveillance or proven therapies specifically targeting SARS-CoV-2, and the medical community had a severely limited understanding of the best ways to manage infected patients.

When the "science" that is to be followed is for the most part uncertain or unknown, academic physicians and research scientists at an academic medical center (AMC) perform a critical role in the survival of effected patients. An AMC is a medical education system that is integrated with a tertiary hospital and clinical facility. The education faculty include a combination of physicians, scientists, and other biomedical personnel that provide the service for the care of patients while simultaneously providing training for future healthcare providers. As experts in their various fields, these faculty frequently are involved in research discovery and the development of cutting-edge medical knowledge. One of the great lessons learned from the experience of the COVID-19 pandemic is the unique role that an AMC can play in response to such a public health emergency.

The following sections provide a partial account of the various ways that the University of Mississippi Medical Center (UMMC) as an AMC met the uncertainties and challenges surrounding the COVID-19 pandemic. A passion for exploring the unknowns is generally what drives research scientists. The same skills and tools that these scientists use in their everyday work was leveraged during this healthcare crisis and proved to be invaluable in the fight against the virus. In this effort, the AMC clearly demonstrated its role in public health crises and the value of those scientists as healthcare heroes.

The Development of a Laboratory-Derived COVID-19 Testing Platform

By late February 2020, It became evident that there was an enormous national demand for commercially available COVID-19 testing materials. Most of the limited supplies were directed toward the larger population centers in the northeastern United States. UMMC leadership decided to develop unique in-house PCR testing capabilities using their new expertise of molecular pathology in conjunction with the advanced instrumentation and experience available in the basic science research laboratories. Within a month, the team had produced a CLIA certified testing platform with the capacity to do hundreds of tests per day to service UMMC patients. This development also helped cover some of the needs for other hospital systems within

the state and provide high throughput COVID-19 testing for the public testing sites operated by the Mississippi Department of Health (MSDH) throughout the state. By late 2020, UMMC was able to routinely run 2000-2500 tests per day.

Production of Sample Collection Kits for COVID-19 Testing

The lack of availability of sample collection kits was also a severe limitation early in the pandemic. The world's supply of sterile swabs for collection of nasopharyngeal samples was consumed before the pandemic reached Mississippi. UMMC researchers and clinicians were able to quickly select an alternative swab and culture medium and validate an in-house sterilization process using equipment in the Department of Surgery. This process required that each swab be individually packaged before being sterilized. Student volunteers from across the campus spent many hours assembling sample collection kits. By the fall of 2020, when commercially prepared kits became available again, UMMC student volunteers had produced over 48,000 kits. Additionally, many of these kits were used at drive through testing sites organized by MSDH.

Initiation of Clinical Trials around Prospective Treatment Regimens

Early in the pandemic, great uncertainty surrounded the best treatment options for patients infected with COVID-19 (Summers & Marshall, 2020). Most of the early clinical trials revolved around one question: should the focus be primarily antiviral or suppression/modulation of the resulting inflammatory response, precipitating the often fatal "cytokine storm" in susceptible patients? Additionally, through an FDA emergency use authorization process, a number of novel therapies emerged. Essentially all treatment regimens were experimental. The UMMC Clinical Trials operations embraced this as a research challenge and began opening new trials and enrolling patients. As of January 1, 2022, UMMC-based investigators have enrolled a total of 1,857 research volunteers into twenty-five different clinical trials funded by various pharmaceutical companies, the National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), the U.S. Department of Defense, the U.S. Health Resources and Services Administration, and local philanthropic organizations including the Robert Hearin Foundation and The John D. Bower Foundation. Collectively, UMMC has received over $5 million in grant funding to conduct these studies, many of which are ongoing. UMMC has also performed clinical trials that have examined the efficacy of thirteen different potential therapies at various stages of COVID-19 from mild symptoms to life threatening respiratory failure in ICU patients with the most severe disease. The endpoints have varied from decreasing mortality risks to shortening symptoms in outpatients with mild to moderate COVID-19. UMMC clinician-scientists also studied immune modulating therapies that are primarily aimed at the immune complications of the COVID-19 clinical illness such as the cytokine storm (a result of dysregulated immunity initiated by the virus but result in end organ damage, especially lung,

heart, liver and kidney, and possible death). Many of these studies offered at least a chance of response in patients with few or no alternative options.

UMMC clinical investigators were involved in several projects with prophylaxis against infection and/or disease development in mind. These were specifically related to immune-based products designed to neutralize the virus (antibody) or provide long lasting antiviral memory T cells, offering long term protection against severe disease. Early antibody-based trials included the evaluation of the effects of plasma obtained from healthy individuals who had recovered from acute COVID-19 (so-called convalescent plasma) when given to severely ill COVID-19 patients. UMMC clinician-scientists were also involved in evaluating the use of monoclonal antibody cocktails on the clinical course of hospitalized moderate to severe COVID-19 patients as well as outpatients. There have even been studies with these monoclonal antibodies as prophylactic agents to prevent infection in close contacts of acute COVID-19 patients. UMMC also participated in the Johnson and Johnson CoV-2 vaccine trial prior to initial approval of the drug for general usage.

Innovative Medical Technologies for Managing Emergency Conditions

Within the first months of the pandemic it was uncertain if there would be enough ventilators to support all the patients requiring assisted respiratory support. At UMMC nearly all of the ventilators were in use for both COVID-19 and other intensive care patients. Dr. Charles Robertson, anesthesiologist, responded to this challenge by developing the Robertson Ventilators made from garden hose sections, adapters, valves, a solenoid, and a lamp timer purchased at local hardware stores for less than $100 dollars per ventilator. The ventilator plugged into the standard oxygen line in a hospital room and could be used in more locations than a standard ventilator. The unique feature of this ventilator was that it controlled airflow from a pressurized oxygen tank using an on-off valve similar to a lawn sprinkler. Further, this was controlled by the timer and the solenoid rather than pushing air into the lungs like traditional ventilators. In preparation for an application for a potential FDA emergency use authorization, the ventilator passed rigorous testing in UMMC research laboratories (simulation center and laboratory animal facility) under broad physiologic conditions and lung pathologies.

Other unique technologies embraced at the beginning of the pandemic include ultraviolet and gas sterilization of Personal Protective Equipment (PPE) for safe reuse during times of supply shortages. Also, 3-D printing devices were used to manufacture alternate nasal swabs while supplied were limited.

Population Health

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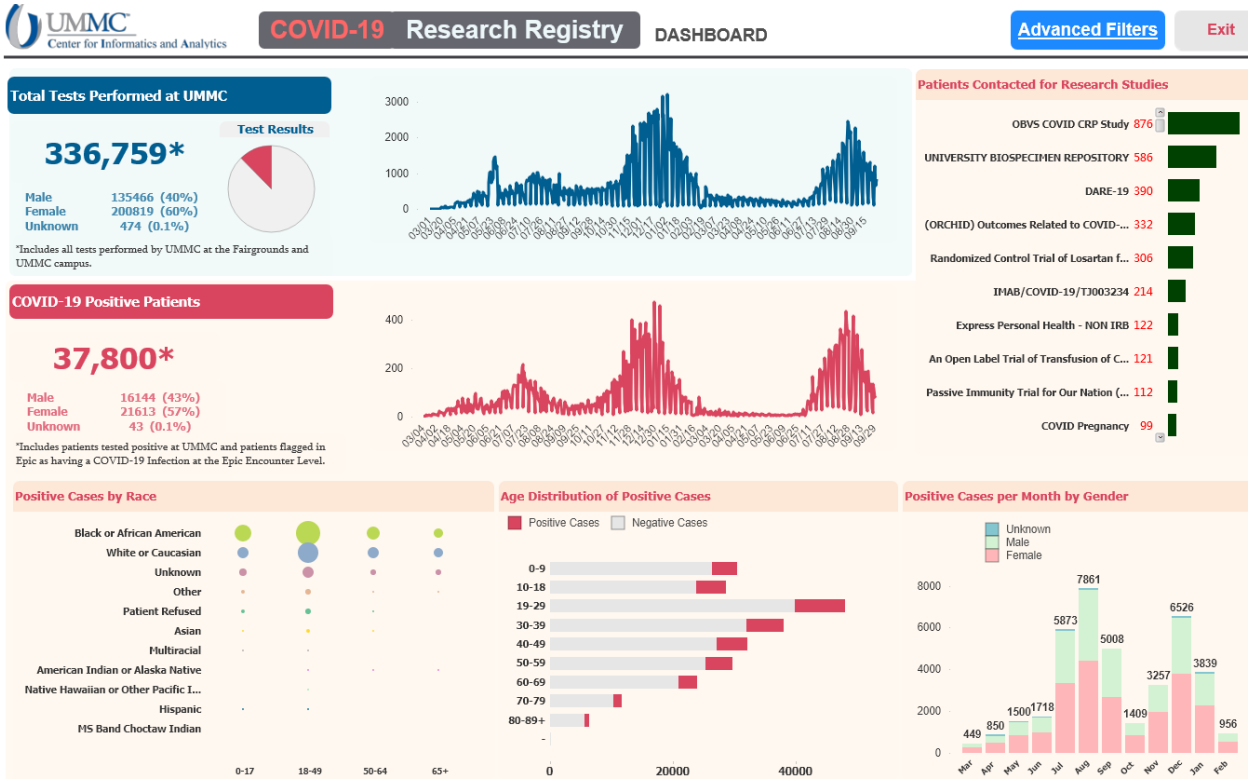
The UMMC Center for Informatics and Analytics along with the UMMC Biobank established COVID-19 specific databases and specimen repositories for use in population studies (See Figure 1). This accumulated information was leveraged to study the impact of COVID-19 on school aged children, perinatal conditions, and the American Indian/Native American demographic (Musshafen et al., 2021). From these information sources, the disease profile and practical social and epidemiological trends associated with the pandemic are being analyzed. They will continue to be utilized to study these conditions and inform us for the future. As the world eventually moves into the post-pandemic period, this information will also be critical to an understanding of long COVID-19 syndromes.

Figure 1

COVID-19 Research Registry and Data Warehouse Dashboard



Telehealth in the Time of COVID

As an AMC, UMMC has been one of the earliest adopters of telehealth in the country, with a rich history of implementing innovative telehealth programs for the past two decades. The earliest example is the TelEmergency Program implemented in 2003 (Summers, et al., 2013). The success of this program led to the expansion of telehealth initiatives within UMMC and, in 2013, the creation of the Center for Telehealth. Since the fall of 2017, the UMMC Center for Telehealth has been recognized as a National Telehealth Center of Excellence by the Health

Resources and Services Administration (HRSA, an agency of the U.S. Department of Health and Human Services) for its implementation of innovative telehealth programs.

Telehealth has long been considered an invaluable tool in healthcare delivery, especially in rural and underserved areas that lack access-to-care. However, during the pandemic Telehealth has proven its value as a valid modality for delivering high quality care to patients of all ages and across all settings including homes, schools, outpatient clinics, hospitals, and skilled nursing facilities. Since the start of the pandemic, the UMMC Center of Telehealth has worked with various clinical departments to provide minimal interruptions in providing care to patients across the state. A brief synopsis of some of the programs that were developed since the start of the pandemic include:

- **COVID -19 Testing**: The UMMC Center for Telehealth contributed to the development of an online mechanism for screening and testing utilized by the Mississippi State Department of Health. Resulting from these efforts, over 400,000 testing appointments have been scheduled since the start of the pandemic.
- **COVID-19 Hotline**: The UMMC Center for Telehealth, in conjunction with the Mississippi State Department of Health, provided telephonic screening of high-risk individuals for testing of COVID-19 throughout the state during the early phase of the pandemic. The telephone hotline is still being utilized by patients to obtain information on vaccination and diagnostic testing in the State.
- **Conserving the Demand of Personal Protective Equipment (PPE)**: As an early response to COVID-19, UMMC created two wings in the Adult Hospital to house all COVID-19 positive patients no longer in the ICU. In an effort to reduce the amount of needed PPE, tablets were placed in the patient rooms that allowed for nurses and physicians to communicate via audio-video with patients without always needing to enter the patient room. This effort conserved a considerable amount of PPE when PPE was in short supply.
- **Outpatient Telehealth Visits**: The UMMC Center for Telehealth developed material to train patients and providers using Telehealth. UMMC rapidly integrated Audio-Video software in the Epic electronic medical record, enabling seamless Telehealth experience for patients and providers. As a result, there was an exponential increase in the number of Telehealth visits for UMMC. The UMMC retrospective data show a growth of more than 950% in ambulatory telehealth visits between 2019 (12,551 telehealth visits) and 2020 (131,903 telehealth visits).
- **Implementing Telehealth Capability in a Field Hospital**: In August 2021, due to the surge in COVID-19 cases in the State, Samaritan's Purse (an international Christian organization) setup a thirty-two-bed field hospital solely for COVID-19 patients in the parking garage. This helped facilitate telehealth consultations by specialists at the main

hospital and remote visitations by family member. The UMMC Center for Telehealth setup audio-video enabled mobile carts in the field hospital.

- **Remote Critical Care Nursing Pilot at UMMC Emergency Department**: To support the bedside staff in the UMMC Emergency Department, the UMMC Center for Telehealth implemented a Telehealth pilot in November 2021. This pilot enabled remote critical care nurses located at Northwell Health, New York to provide monitoring of critically ill patients boarding in the ED and support the bedside nursing staff using audio-video technology.
- **TeleUrgent Care Program**: In response to COVID-19, the TeleUrgent Care program at the UMMC Center for Telehealth is offering remote consultations directly to patients in their homes throughout the State. In addition to providing care to patients at home, it should reduce unnecessary visits to the emergency department for mild cases, which can be managed at home.

After the initial stages of the pandemic but before the Delta surge, the comparative rapid rise in telehealth visits experienced at UMMC as in-person visits waned (See Figure 2). One of the very few benefits that will be realized from the pandemic experience is that a new perspective concerning the role of telehealth in public health now exists.

Figure 2

C*hange in Volume of Telehealth Utilization by UMMC Providers in the First Year of the Pandemic.*

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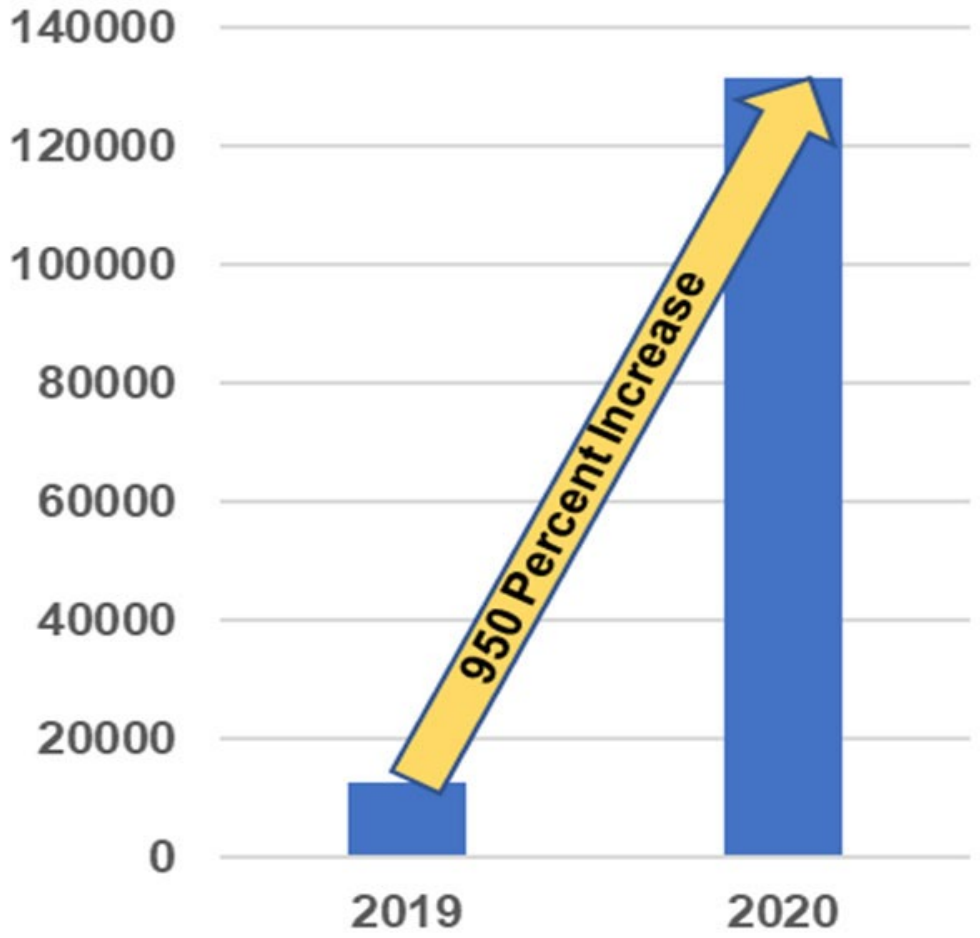

Biosurveillance

Whole Genome Sequencing of SARS-CoV-2

Before Delta and Omicron variants emerged, the UMMC Genomics team began to consider tracking virus mutations and strains across the state. As early as March 2020, the groundwork to establish whole genome sequencing of SARS-CoV-2 began, and samples from the Clinical Genomics Laboratory housed in the UMMC Department of Pathology were collected. The establishment of a sample collection pipeline involved a group of both clinical faculty and staff, the UMMC Center for Informatics and Analytics (CIA) to provide basic demographics on the samples (sex, age, race, city, and county), and basic science researchers to sequence the samples and interpret the results (See Figure 3).

Figure 3
COVID-19 Sample Collection Pipeline and Workflow

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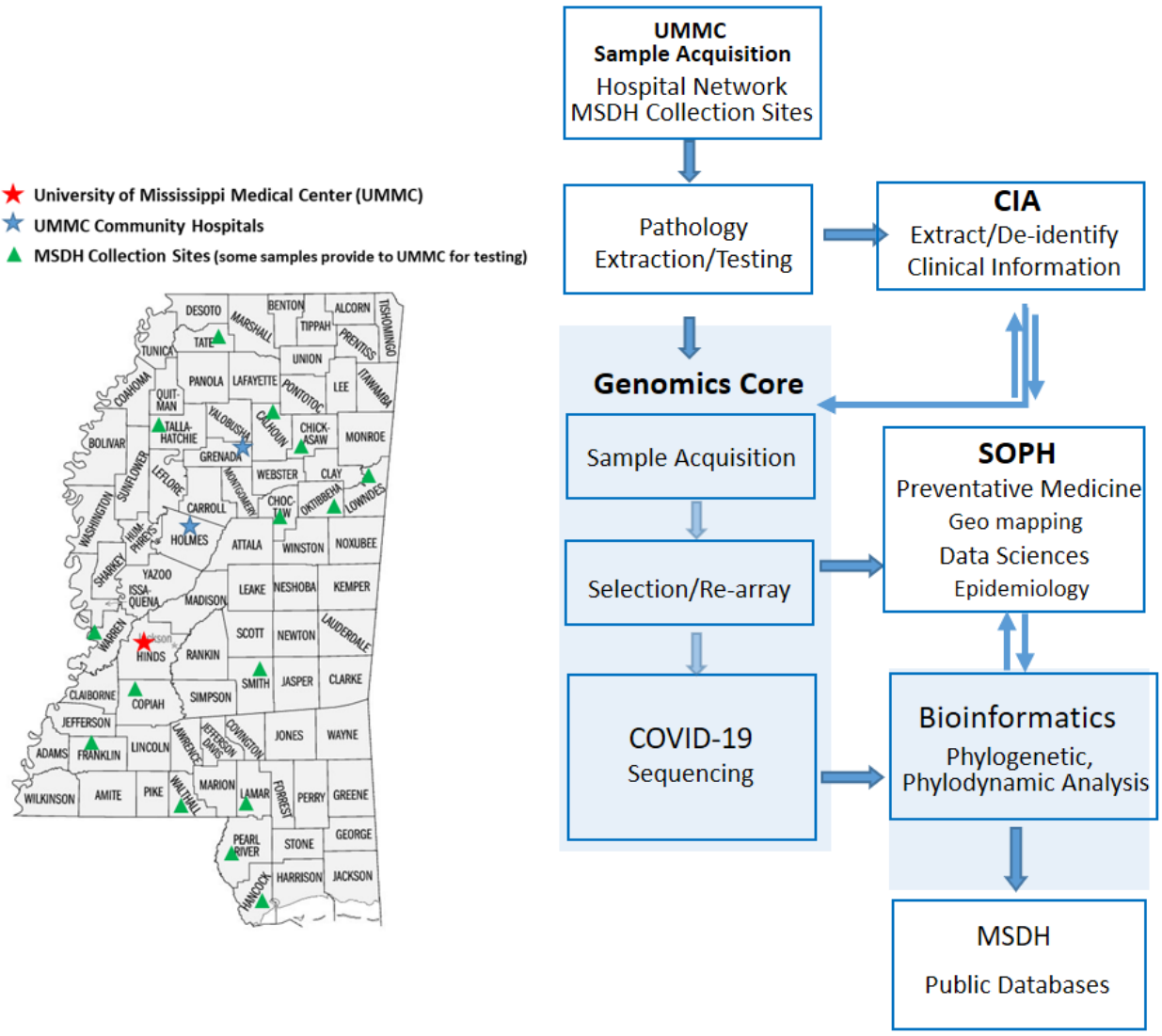

Of the >100,000 samples that underwent diagnostic testing for SARS-CoV-2 between May 1 and December 21, 2020, more than 8,000 positive samples were collated and archived pending sequencing. The samples covered 81/82 (99%) counties in Mississippi, with most samples being from Hinds county (Jackson, MS metropolitan area), the largest number of samples by county in Mississippi (n=2,511) and two surrounding counties (Madison=566, Rankin=601), except for De Soto county (n=431) which is located in a geographically distinct region bordering Tennessee in northern Mississippi. The number of samples available for other counties were 0-10 samples (5), 11-20 samples (12), 21-50 samples (30), 51-100 samples (21), and 101-250 samples (10). Between May and June, a number of technologies and sequencing approaches were assessed to determine the optimal sequencing approach, and by June 2020 a successful pilot study generated whole genome sequencing data of SARS-CoV-2. Sample collection continued through the end of December, at which time several potential funding opportunities arose that would provide resources to sequence the archived samples as well as collect samples in real-time for SARS-

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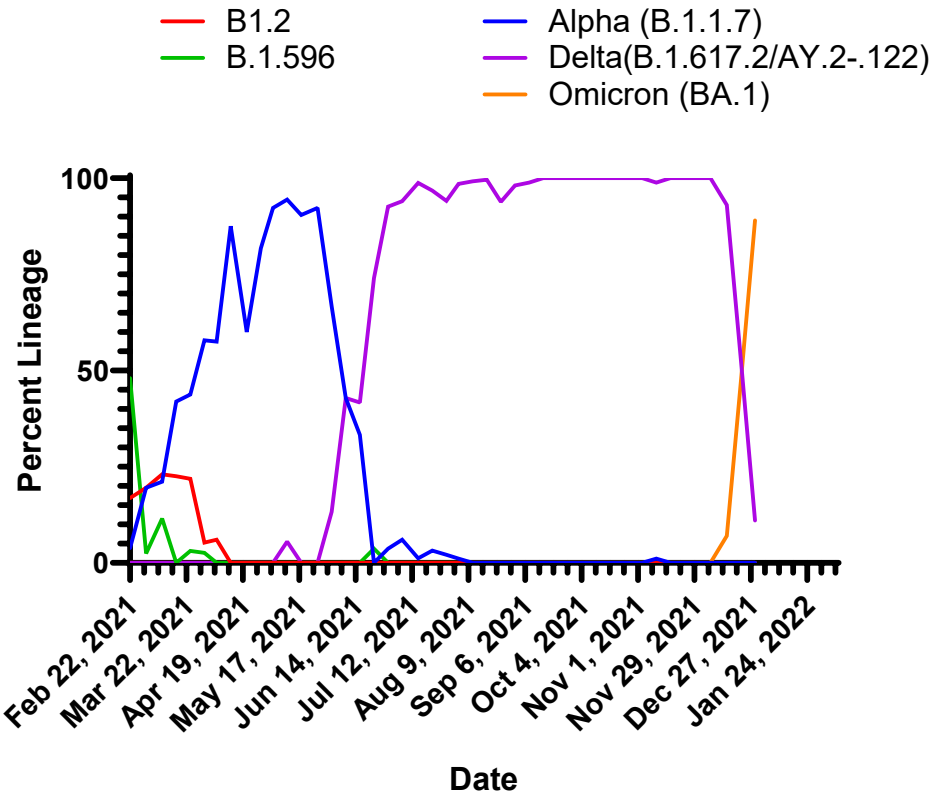
CoV-2 sequencing biosurveillance. By March 1, 2021, the biosurveillance program began via a contract with the MSDH, and by June 1, 2021, additional resources were acquired from the CDC to begin sequencing of the archived samples as well as supplement MSDH biosurveillance. By December 2021, UMMC had sequenced more than 6,000 samples through support of the MSDH and CDC, which represented ~50% of the total number of sequences available in public databases for Mississippi samples. These efforts captured the rise of the Alpha, Delta, and Omicron variants in the state (See Figure 4).

Figure 4

Tracking of SARS-CoV-2 Lineages through Biosurveillance Projects



Evinced by current events, tracking variants is more than just an academic exercise and can be used to identify lineages of emerging public health concern. In July 2021, the UMMC sequencing team identified a unique variant not previously catalogued in the GISAID database. The variant was found to be a sub-lineage of the AY.3 Delta strain, which in turn was a sub-lineage of the B.1.617.2 common strain (See Figure 5). The evidence for this new variant was submitted to the International Pangolin Lineage Naming Committee and was officially designated as AY.3.1 (B.1.617.2.3.1) and locally termed the “Mississippi” variant. By the end of the Delta wave, AY.3.1 represented 17% of all SARS-CoV-2 sequences from Mississippi, compared to 1-3% of sequences from surrounding states.

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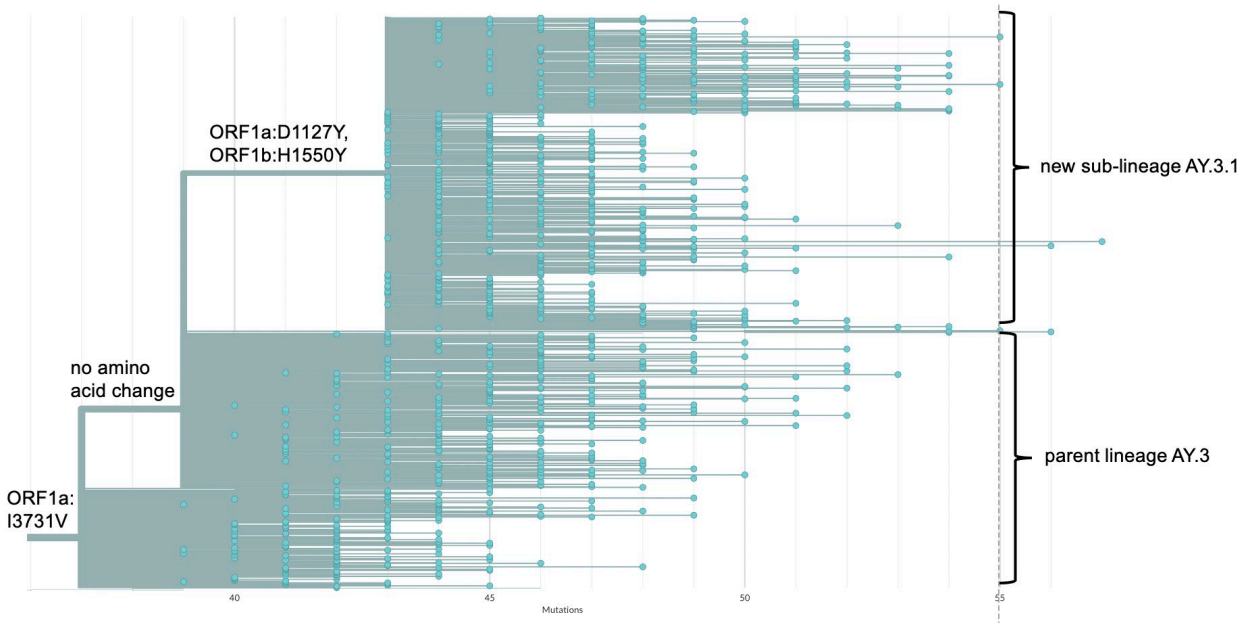
Figure 5

Identification of the Unique "Mississippi" Variant, AY.3.1



Antibody Biosurveillance

UMMC clinical scientists have also been engaged in several studies intending to better understand the course of the infection and factors that influence clinical outcomes in a variety of patient populations. These researchers participated in several studies that collect data on rapid testing and demonstrated how it compares to the more sensitive but very laborious and laborious molecular genetic testing. Furthermore, laboratory specialists have methodically collected biological samples from 487 COVID-19 patients and stored them in the UMMC Biobank for distribution of scientists to answer such questions as the amount of neutralizing anti-CoV-2 antibody in patients who have recovered from COVID-19 vs those vaccinated against the virus (Mahajan, 2021). During an in-house study, 783 UMMC employees received repeated blood draws over the past eighteen months to understand how virus-specific antibody and memory T cells fare over time after vaccination and more recently with boosters.

The Future: Long COVID and the Forgotten Patient

Once the state of COVID-19 has shifted from a pandemic to an endemic status, healthcare workers will begin being faced with the long-term impact of this crisis on individual patients infected with the virus. UMMC physicians are already beginning to see patients with a myriad of complaints such as neurological symptoms, cardiac conditions, and chronic respiratory problems associated with a prior COVID-19 infection. However, these conditions, collectively known as Post-COVID or Long COVID syndrome (PASC), are yet to be clearly defined and much less

understood. In an attempt to better understand the future impact of the pandemic, NIH has sponsored the RECOVER Study of Long COVID in Adults. RECOVER is a combined retrospective and prospective, longitudinal, observational meta-cohort of individuals who will enter the cohort with and without SARS-CoV-2 infection at varying stages before and after infection. Individuals with and without SARS-CoV-2 infection and with or without PASC symptoms will be followed to identify risk factors and occurrence of PASC. The intent is to:

- Characterize the incidence and prevalence of sequelae of SARS-CoV-2 infection.
- Identify clinical symptoms, organ dysfunction, natural history, and phenotypes.
- Define the biological mechanisms underlying pathogenesis of the sequelae.

UMMC is a site for this national study and is currently collecting data. Ancillary studies for RECOVER concerning interventional treatments will be forthcoming and UMMC researchers are planning such studies.

Conclusion

From access to diagnostics to treatment to biosurveillance, the AMC has demonstrated its critical role during the COVID-19 pandemic. The knowledge drawn from this experience should hopefully benefit in times of future crises. While many of these clinical-research crossover functions are not routinely engaged by an AMC, it is important that the state of Mississippi have a supported infrastructure in place to rapidly respond when it is needed during a public health emergency.

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